Central Administration of Pharmaceutical Care
General Administration for Drug Utilization and Pharmacy Practice

Egyptian National Drug Formulary

Conventional Anticancer Drugs

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Preface

The Egyptian Drug Formulary is published by the Egyptian Drug Authority, the Central Administration of Pharmaceutical Care, by the General Administration of Drug Utilization and Pharmacy Practice. It has been discussed within the Committee for Oncology Pharmacy Practice.

The Egyptian Drug Formulary aims to provide pharmacists and other healthcare professionals with accessible and reliable information about the available medications in the Egyptian drug database for making the right clinical decisions.

The Egyptian Drug Formulary is a guide that should be interpreted in light of professional knowledge. The developers work to ensure that the information is as accurate and up-to-date as possible at the date of publication but knowledge and best practice change regularly. No responsibility for the work team for errors or omissions.

Egyptian National Drug Formulary Manual

(Conventional Anticancer Drugs)

The Egyptian National Drug Formulary (Conventional Anticancer Drugs) contains a list of medicines registered in the Egyptian drug database included in the essential medicines list or widely used on the Egyptian pharmaceutical market. It is designed as drug monographs classified pharmacologically and arranged alphabetically. There is a pharmacologically classified drug index at the beginning of the document and another alphabetically classified index at the end.

Conventional Anticancer Drugs chapter of Egyptian National Drug Formulary presents detailed practical information for healthcare providers about each medicine.

Each monograph includes:

1. Generic name.
2. Dosage form/strengths available in Egypt from the EDA database.
3. Route of administration.
4. Pharmacological category and ATC code.
5. Indications: Approved indications by drug authorities.
6. Dosage regimens for adults and children.
7. Dosage adjustments if needed.
8. Contraindications.
9. Adverse drug reaction.

10. Monitoring parameters.
11. Drug Interactions: that imply avoidance or considering modifications.
12. Pregnancy and lactation.
13. Administration: Detailed administration information for all routes [parenteral (preparation, compatibility with diluents, infusion rate, precautions during administration), Oral (food correlation)].
14. Emetogenicity: Incidence of emesis in absence of prophylaxis.
15. Warnings/Precautions.
16. Storage and Light Sensitivity.

- For reconstituted vials, apply mentioned storage conditions only if prepared in aseptic techniques and ISO-controlled conditions according to USP 797 standards, otherwise discard immediately if not used.
- USP develops standards for compounding medications to help ensure patient benefit and reduce risks such as contamination, infection, or incorrect dosing.

17. Patient counselling keys.

18. Sequence of administration:

    Considerations for administration sequence of parenteral antineoplastic drugs that is administered on the same day:

    - Cycle-specific antineoplastic agents in infusion are recommended to be administered before cycle-nonspecific agents. This is supposed to maximize effect in cells with high cell division rates, as neoplastic cells.

- Administer the vesicant antineoplastic drug first, as vascular integrity decreases with time. It is therefore advantageous to infuse the vesicant antineoplastic agent when the vein is more stable and less irritated.
- Consider the less toxic agent first.

19. Pharmaco-genomics: Gene considerations if any.

Refer to manufacturer PIL (Patient Information Leaflet) and SPC (Summary of product characteristics) if there are other specific consideraions.

Conventional Anticancer Drugs Formulary

This document includes medications that contribute in management of malignant tumors.

Therapeutic classes include: Alkylating Agents, Antimetabolites, Antimicrotubule Agents, Cytotoxic Antibiotics, Hormonal Therapies, Immune Modulatory Drug, Therapeutic enzymes, Topoisomerase Inhibitors, Retinoids, Supportive Medicines and Miscellaneous.

Acknowledgment

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Finally, we would like to thank EDA's staff for their hard work and dedication to this project.

Disclaimer

Any information about drugs mentioned inside this formulary is general, and does not cover all data of the medications included. The content is not intended for use as medical advice for individual problems or for evaluating the risks and benefits of taking a particular drug. Generally, all knowledge and best practices are subject to frequent changes and updates.

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ALKYLATING AGENTS

A. Alkyl Sulfonates

1. Busulfan

Generic name	Busulfan
Dosage Forms/ Strengths	Enteric-coated tablets: 2mg.
Route of Administration	Oral.
Pharmacologic Category	Antineoplastic Agent, Alkylating Agent. ATC Code: L01AB01.
Indications	**N.B.** *Refer to literature and specific protocols for all indications.* • Palliative treatment of chronic myelogenous (myeloid, myelocytic, granulocytic) leukemia.
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols.* • **Adult and pediatric dosing:** **Oral**: 60 mcg/kg or 1.8 mg/m^2 of body surface, daily. • **The usual adult dose** range for remission induction is 4 to 8 mg, total dose, daily.
Dosage Adjustment	**N.B.** Refer to the protocol used for specific dose modifications. • **Altered Kidney Function: Adult and pediatric:** Specific guidelines for dosage adjustments in renal impairment are not available; initial dosage adjustments may not be needed. **Hepatic Impairment: Adult and pediatric** Specific guidelines for dosage adjustments in hepatic impairment are not available; initial dosage adjustments may not be needed.
Contra-indications	• Hypersensitivity to busulfan or any component of the formulation. • Patients without a definitive diagnosis of chronic myeloid leukemia.
Adverse Drug Reactions	**1% to 10%:** • **Central nervous system**: Seizure (2%; despite prophylactic antiseizure therapy). • **Dermatologic**: Skin hyperpigmentation (5% to 10%). • **Hematological Effects:** The most frequent, serious, toxic effect of busulfan is dose-related myelosuppression resulting in leukopenia, thrombocytopenia, and anemia. • **Hepatic Effects**: Esophageal varices have been reported in patients receiving continuous busulfan and thioguanine therapy for the treatment of chronic myelogenous leukemia. **Frequency not defined:** • **Endocrine & metabolic**: Amenorrhea, ovarian failure. • **Respiratory**: Pulmonary interstitial fibrosis.

Monitoring Parameters	• CBC with differential and platelet count. • Liver function tests. • Monitor for signs/symptoms of cardiac tamponade, sinusoidal obstruction syndrome, infection, and bleeding.
Drug Interactions	• ***Risk X: Avoid combination:*** Abrocitinib, Baricitinib, BCG Products, Brivudine, Chikungunya Vaccine (Live), Chloramphenicol (Systemic), Cladribine, Dengue Tetravalent Vaccine (Live), Deucravacitinib, Dipyrone, Etrasimod, Fexinidazole, Filgotinib, Mumps-Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Poliovirus Vaccine (Live/Trivalent/Oral), Ritlecitinib, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Typhoid Vaccine, Upadacitinib, Vaccines (Live), Yellow Fever Vaccine. • ***Risk D: Consider therapy modification*** Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), Deferasirox, Deferiprone, Denosumab, Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Metronidazole (Systemic), Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating).
Pregnancy and Lactation	**Pregnancy**: Busulfan may cause fetal harm when administered to a pregnant woman. No adequate and well-controlled studies in pregnant women. High risk of temporary or permanent infertility for men and women. **Lactation**: Not recommended due to potential hazard to the infant.
Administration	• **Hazardous agent (NIOSH 2016 [group 1]):** Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. • **Administration: Oral** ○ May be administered without regard to meals. ○ Antiemetics may be recommended to prevent nausea and vomiting. N.B. Refer to manufacturer PIL for specific considerations.
Emetogenicity	**Adults** ○ Oral ≥4 mg/day: Moderate or high (≥30%). ○ Oral <4 mg/day: Minimal or low (<30%). **Pediatrics** ○ Oral: ≥1 mg/kg/dose: High (>90%).
Warnings/ Precautions	**Bone marrow suppression** Severe and prolonged bone marrow suppression commonly occurs. May result in severe neutropenia, thrombocytopenia, anemia, bone marrow failure, and/or severe pancytopenia; pancytopenia may be prolonged (1 month up to 2 years) and may be reversible. **Cardiovascular:** Cardiac tamponade has been reported in children with thalassemia treated with

	high-dose oral busulfan in combination with cyclophosphamide. Abdominal pain and vomiting preceded tamponade in most children. **Hepatic veno-occlusive disease:** Oral busulfan doses above 16 mg/kg (based on IBW) and concurrent use with alkylating agents may increase the risk for hepatic veno-occlusive disease. **Pulmonary toxicity:** Chronic Busulfan use is associated with bronchopulmonary dysplasia with pulmonary fibrosis ("Busulfan lung"); onset is delayed (average 4 years, range: 4 months to 10 years) after treatment; may be fatal. Symptoms generally include a slow onset of cough, dyspnea, and fever (low-grade), although acute symptomatic onset may also occur. Busulfan should be discontinued if this lung toxicity develops. **Tissue dysplasia:** Cellular dysplasia in many organs has been observed (in addition to lung dysplasia). **Secondary malignancies:** Tumors and acute leukemias have been reported following use. Chromosomal alterations may also occur. **Seizures:** Seizures have been reported with high-dose oral Busulfan.
Storage and Light Sensitivity	• Keep between 15°C and 30°C. • Protect from light. **N.B.** Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• This medicine alters blood counts. Check your blood counts regularly and avoid causes of infection and bleeding. • This drug may raise the chance of seizures in some people, including people who have had seizures in the past. Talk to your doctor to see if you have a greater chance of seizures while taking this drug. • A very bad and sometimes deadly heart problem has happened with some people taking this drug. Most of the time, stomach pain and throwing up happened before the heart problem. Talk with the doctor. • Call your doctor right away if you have signs of lung problems like shortness of breath or other trouble breathing, cough that is new or worse, or fever.

B. Nitrogen Mustard Agents

1. Bendamustine

Generic name	Bendamustine
Dosage Forms/ Strengths	Powder for concentrate for solution for infusion: 25mg, 100mg
Route of Administration	IV
Pharmacologic Category	Antineoplastic Agent, Alkylating Agent ATC code: L01AA09
Indications	**N.B.** *Refer to literature and specific protocols for all indications.* • Chronic lymphocytic leukemia. • Indolent B-cell non-Hodgkin lymphoma (NHL). • Front-line treatment of multiple myeloma
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols.* **Adult Dosing:** • **Monotherapy for chronic lymphocytic leukemia:** 100 mg /m^2 body surface area bendamustine hydrochloride on days 1 and 2; every 4 weeks up to 6 times. • **Monotherapy for indolent non-Hodgkin´s lymphomas** refractory to rituximab: 120 mg/m^2 on days 1 and 2; every 3 weeks for at least 6 times, up to 8 cycles. • **Multiple myeloma:** 120-150 mg/m^2 on days 1 and 2, Prednisone 60 mg /m^2 IV or Oral on days 1 to 4; every 4 weeks for at least 3 times. **Pediatric dosing:** The effectiveness of bendamustine in pediatric patients has not been established.
Dosage Adjustment	**N.B.** *Refer to the protocol used for specific dose modifications.* **Hepatic impairment:** • Mild hepatic impairment: No dose adjustment is necessary. • Moderate hepatic impairment (serum bilirubin 1.2 - 3.0 mg/dl): A 30% dose reduction may be used. • Avoid use with (AST or ALT 2.5-10 X ULN and total bilirubin 1.5-3 X ULN) **Renal impairment:** • Creatinine clearance of < 30 ml/min: Not recommended. No sufficient data. **Non-hematological toxicity:** According to the preceding cycle, modifications apply to days 1, and 2 of the following cycle: • Toxicity grade 3: 50% dose reduction is recommended. • Toxicity grade 4: Interrupt treatment.

	Hematologic toxicity: • Grade 3 or greater toxicity, reduce dose to 50 mg/m^2 on Days 1 and 2. • Grade 3 or greater toxicity recurs, reduce dose to 25 mg/m^2 on Days 1 and 2.
Contra-indications	• Hypersensitivity to the active substance or any of the excipients. • Severe hepatic impairment (serum bilirubin > 3.0 mg/dl), Jaundice. • Severe bone marrow suppression and severe blood count alterations (leukocyte and/or platelet values dropped to < 3 ˣ10^9 /l or < 75 ˣ10^9 /l, respectively) • Infections, especially involving leukocytopenia
Adverse Drug Reactions	**>10%** **Cardiovascular**: Peripheral edema (13%). **Dermatologic**: Skin rash (8% to 16%). **Endocrine & metabolic**: Dehydration (14%), weight loss (7% to 18%). **Gastrointestinal**: Abdominal pain (13%), anorexia (23%), constipation (29%), decreased appetite (13%), diarrhea (9% to 37%; grades 3/4: 1% to 3%), dyspepsia (11%), nausea (20% to 75%; grades 3/4: ≤4%), stomatitis (15%; grades 3/4: <1%), vomiting (16% to 40%; grades 3/4: ≤3%). **Hematologic & oncologic:** Bone marrow depression (grades 3/4: 98%), decreased hemoglobin (88% to 89%; grades 3/4: 11% to 13%), decreased neutrophils (75% to 86%; grades 3/4: 43% to 60%), decreased platelet count (77% to 86%; grades 3/4: 11% to 25%), leukopenia (61% to 94%; grades 3/4: 28% to 56%), lymphocytopenia (68% to 99%; grades 3/4: 47% to 94%). **Hepatic**: Increased serum bilirubin (34%). **Nervous system**: Asthenia (8% to 11%), chills (6% to 14%), dizziness (14%), fatigue (9% to 57%), headache (21%), insomnia (13%). **Neuromuscular & skeletal:** Back pain (14%). **Respiratory**: Cough (4% to 22%), dyspnea (16%). **Miscellaneous**: Fever (24% to 34%). **1% to 10%** **Cardiovascular**: Chest pain (6%), exacerbation of hypertension (3%; including hypertensive crisis), hypotension (6%), tachycardia (7%). **Dermatologic**: Hyperhidrosis (5%), night sweats (5%), pruritus (5% to 6%), xeroderma (5%). **Endocrine & metabolic**: Hyperglycemia (grades 3/4: 3%), hyperuricemia (7%), hypocalcemia (grades 3/4: 2%), hypokalemia (9%), hyponatremia (grades 3/4: 2%). **Gastrointestinal**: Abdominal distention (5%), dysgeusia (7%), gastroesophageal reflux disease (10%), oral candidiasis (6%), upper abdominal pain (5%), xerostomia (9%). **Genitourinary**: Urinary tract infection (10%). **Hematologic & oncologic**: Febrile neutropenia (6%). **Hepatic**: Increased serum alanine aminotransferase (grades 3/4: 3%), increased

	serum aspartate transaminase (grades 3/4: 1%). **Hypersensitivity**: Hypersensitivity reaction (5%). **Infection**: Herpes simplex infection (3%), herpes zoster infection (10%), infection (6%). **Local**: Infusion-site pain (6%). **Nervous system**: Anxiety (8%), depression (6%), pain (6%). **Neuromuscular** & **skeletal**: Arthralgia (6%), limb pain (5%), ostealgia (5%). **Renal**: Increased serum creatinine (grades 3/4: 2%). **Respiratory**: Nasal congestion (5%), nasopharyngitis (6% to 7%), pharyngolaryngeal pain (8%), pneumonia (8%; including atypical pneumonia), sinusitis (9%), upper respiratory tract infection (10%), wheezing (5%).
Monitoring Parameters	• CBC with differential and platelets. • Liver and Kidney functions (before and during treatment). • Monitor the IV site during and after infusion. • Monitor potassium and uric acid levels. • Monitor for signs/symptoms of infusion reactions, anaphylaxis, infection (including reactivations), dermatologic toxicity, progressive multifocal leukoencephalopathy, and tumor lysis syndrome. • Monitor for the development of secondary malignancies.
Drug interactions	***Risk X: Avoid combination*** BCG (Intravesical), Cladribine, Dipyrone, Fexinidazole ***Risk D: Consider therapy modification*** CYP1A2 Inducers (Moderate), CYP1A2 Inhibitors (Moderate), CYP1A2 Inhibitors (Strong), Deferiprone, Lenograstim, Lipegfilgrastim, Palifermin, Ropeginterferon Alfa-2b **N.B** Inhibitors of CYP1A2 (e.g., fluvoxamine, ciprofloxacin, acyclovir, or cimetidine) have the potential to decrease plasma concentrations of active metabolites. Inducers of CYP1A2 (e.g., omeprazole, smoking) have the potential to increase plasma concentrations of its active metabolites.
Pregnancy and lactation	**Pregnancy**: Contraindicated in 1st trimester. No sufficient human data. Women should not become pregnant during treatment. Male patients should not father a child during and up to 6 months after treatment. Irreversible infertility may occur. **Lactation**: Contraindicated. No sufficient data.
Administration	• **Hazardous Drugs Handling Considerations:** Hazardous agent (NIOSH 2016 [group 1]): Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. • **IV infusion**: over 30 to 60 minutes. • Consider premedication with antihistamines, antipyretics, and corticosteroids for patients with a previous grade 1 or 2 infusion reaction to bendamustine. • Vesicant.

	• **Extravasation management:** If extravasation occurs, stop infusion immediately and disconnect (leave cannula/needle in place); gently aspirate extravasated solution (do NOT flush the line); remove needle/cannula; elevate extremity. Apply dry cold compresses for 20 minutes 4 times daily. May be managed with sodium thiosulfate. **Preparation for Administration: Adult** • Reconstitute 25 mg vial with 5 mL and 100 mg vial with 20 mL of sterile water for injection to a concentration of 5 mg/mL; powder usually dissolves within 5 minutes (do not use if particulates are visible). Within 30 minutes of reconstitution, dilute the appropriate dose for infusion in 500 mL NS to a final concentration of 0.2 to 0.6 mg/mL. N.B. Refer to manufacturer PIL for specific considerations.
Emetogenicity	**Moderate emetic risk:** (>30%–90% frequency of emesis).
Warnings/ Precautions	• **Myelosuppression**: Monitor leukocytes, platelets, hemoglobin, and neutrophils at least weekly. Before the initiation of the next cycle of therapy, the following parameters are recommended: Leukocyte and/or platelet values > 4^{x} 10^{9}/l or > 100^{x} 10^{9}/l, respectively. • **Infections:** Serious and fatal infections have occurred with bendamustine hydrochloride, including bacterial (sepsis, pneumonia) and opportunistic infections. • **Skin reactions:** These events have included rash, severe cutaneous reactions, and bullous exanthema. If skin reactions are progressive, Bendamustine should be withheld or discontinued. For severe skin reactions treatment should be discontinued. • **Secondary malignancy:** including myelodysplastic syndrome and non-melanoma skin cancer. Periodic examination is recommended for all patients. • **Cardiac disorders:** Fatal cases of myocardial infarction and cardiac failure have been reported. Monitor blood potassium must be closely monitored, and potassium supplement must be given when K^{+}<3.5mEq/l. • **Tumour lysis syndrome:** Preventive measures such as adequate hydration, close monitoring of blood potassium and uric acid levels, and the use of hypouricemic agents (allopurinol) should be considered before therapy. • **Anaphylaxis:** Symptoms are generally mild and include fever, chills, pruritus, and rash. In rare instances, severe anaphylactic and anaphylactoid reactions have occurred. • **Hepatotoxicity:** Fatal and serious cases of liver injury occurred. Combination therapy, progressive disease or reactivation of hepatitis B were confounding factors in some patients.
Storage and Light	• Store intact vials 25°C -30^{0}C. • Protect from light.

Sensitivity	• The solution in the vial (reconstituted with SWFI) is stable for 30. • The solution diluted in 500 mL of NS for infusion is stable for 24 hours refrigerated (2°C to 8°C) or 3 hours at room temperature (15°C to 30°C) and room light. Infusion must be completed within these time frames. **N.B.** Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• This medicine may lower blood count. Avoid causes of infection and bleeding. • Call your doctor if you develop allergic reactions, or heart, or liver disorders (chest pain; swelling in the extremities, abnormal heartbeat; shortness of breath, tiredness, decreased appetite, or yellow skin or eyes. • Bendamustine is teratogenic and mutagenic. Avoid getting pregnant during administration. Irreversible infertility may occur.
Sequence of Administration	• Vesicant. • Cell cycle-specfic S phase. • Vesicant and cell cycle-specific agents are given first.

2. Chlorambucil

Generic Name	Chlorambucil
Dosage Forms/ Strengths	Tablet: 2mg
Route of Administration	Oral
Pharmacologic Category	Antineoplastic Agent, Alkylating Agent (Nitrogen Mustard) ATC code: L01AA02
Indications	**N.B.** *Refer to literature and specific protocols for all indications.* • Hodgkin's disease • Certain forms of non-Hodgkin's lymphoma e.g. lymphosarcoma, giant follicular lymphoma. • Chronic lymphocytic leukemia. • Waldenstrom's macroglobulinemia.
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols.* **Adult dosing**: Round the dose to the nearest 2 mg. **Hodgkin's disease:** 0.2 mg/kg/day for 4-8 weeks. Used as a single agent in the palliative treatment of advanced disease or combination therapy. **Non-Hodgkin's lymphoma:** used as a single agent. • Usual initial dose: 0.1-0.2 mg/kg/day for 4-8 weeks. • Maintenance therapy: Reduced daily dosage or intermittent courses of treatment. **Chronic lymphocytic leukemia:** • Initial: 0.15 mg/kg/day until the total leucocyte count reaches 10,000 per µL. • Resume for 4 weeks, after that continue a dosage of 0.1 mg/kg/day. Used in impaired bone marrow function. Patients with evidence of bone marrow failure should first be treated with prednisolone till marrow regeneration. **Waldendstrom's macroglobulinemia:** • Initial: 6-12 mg daily until leukopenia occurs. • Maintenance therapy: 2-8 mg daily indefinitely. **Pediatric dosing:** May be used in Hodgkin's disease or non-Hodgkin's lymphoma: the same as adult dosing.
Dosage Adjustment	**N.B.** *Refer to the protocol used for specific dose modifications.* **Dosing: Altered Kidney Function: Adult**

	No dose adjustment is necessary. **Dosing: Hepatic Impairment: Adult** • Primarily metabolized in the liver • Moderate hepatic impairment: close monitor for signs and symptoms of toxicity. • Severe hepatic impairment: dose modifications are recommended. Data is insufficient. **Elderly:** Caution. Monitor renal and hepatic functions. Initiate therapy at the low end of the dosage range **Dosing: Adjustment for Toxicity:** • Skin reactions: Discontinue treatment. • Hematologic toxicity: - WBC or platelets below normal: Reduce dose. - Severely depressed WBC or platelet counts: Discontinue. - Persistently low neutrophil or platelet counts or peripheral lymphocytosis: May be suggestive of bone marrow infiltration; if infiltration is confirmed, do not exceed 0.1 mg/kg/day.
Contra-indications	• Hypersensitivity to chlorambucil or any of the excipients. • There may be cross-hypersensitivity (skin rash) between chlorambucil and other alkylating agents. • Prior resistance for chlorambucil.
Adverse drug Reactions	**≥10%:** • Blood and lymphatic system: Leukopenia, neutropenia, thrombocytopenia, pancytopenia, or bone marrow suppression. **≥1%:** • Neoplasms benign, malignant, and unspecified (including cysts and polyps): Acute secondary hematologic malignancies (especially leukemia and myelodysplastic syndrome), particularly after long-term treatment. • Blood and lymphatic system: Anemia • Nervous system: Convulsions in children with nephrotic syndrome • Gastrointestinal disorders: Gastrointestinal disorders such as nausea and vomiting, diarrhea, and mouth ulceration. **Frequency not defined.** • Central nervous system: Drug fever, peripheral neuropathy • Dermatologic: Allergic skin reaction, skin rash, urticaria • Endocrine & metabolic: Amenorrhea • Gastrointestinal: Diarrhea (infrequent), nausea (infrequent), oral mucosa ulcer (infrequent), vomiting (infrequent) • Genitourinary: Azoospermia, cystitis (sterile), infertility

	• Hematologic & oncologic: Anemia, bone marrow depression, bone marrow failure (irreversible), leukemia (secondary), leukopenia, lymphocytopenia, malignant neoplasm (secondary), neutropenia (onset: 3 weeks; recovery: 10 days after last dose), pancytopenia, thrombocytopenia • Hepatic: Hepatotoxicity, jaundice • Hypersensitivity: Angioedema, hypersensitivity reaction • Respiratory: Interstitial pneumonitis, pulmonary fibrosis • Miscellaneous: Fever
Monitoring Parameters	• CBC with differential • Liver function test
Drug Interactions	***Risk X: Avoid combination*** Abrocitinib, Baricitinib, BCG (Intravesical), BCG Products, Brivudine, Cladribine, Dengue Tetravalent Vaccine (Live), Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Mumps- Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Poliovirus Vaccine (Live/Trivalent/Oral), Ritlecitinib, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Typhoid Vaccine, Upadacitinib, Vaccines (Live), Yellow Fever Vaccine ***Risk D: Consider therapy modification*** Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), Deferiprone, Denosumab, Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating)
Pregnancy and Lactation	**Pregnancy:** Mutagenic and teratogenic in humans. Adverse renal effects (unilateral agenesis) in the newborn if taken first trimester**.** Reversible and irreversible sterility in adult males or females) have been observed. **Lactation:** Not recommended due to the potential for serious adverse reactions**.**
Administration	**Oral**: Taken daily on an empty stomach (at least one hour before meals or three hours after meals). **Hazardous agent** (NIOSH 2016 [group 1]): Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. Carcinogen. Pregnancy Category D. N.B. Refer to manufacturer PIL for specific considerations.
Emetogenicity	Minimal to low emetic risk (<30% frequency of emesis)
Warnings/ Precautions	**Bone marrow suppression:** Chlorambucil may cause severe bone marrow suppression but is usually reversible. **Secondary malignancy**: Chlorambucil is a human carcinogen. **Seizures**: Reported in patients with nephrotic syndrome, high pulse doses and a history of seizure disorder are at higher risk of seizures. Use with caution in these patients.

	Skin reactions: Skin rash has been reported rarely to progress to serious conditions including Stevens-Johnson syndrome and toxic epidermal necrolysis; discontinue promptly if skin reaction occurs. **Reversible Severe interstitial pulmonary fibrosis** has occasionally been reported in patients with chronic lymphocytic leukemia on long-term Chlorambucil therapy. **Hepatic impairment**: Chlorambucil is primarily metabolized in the liver. Dosage reductions should be considered in patients with hepatic impairment. **Vaccines**: Avoid administration of live vaccines to immunocompromised patients.
Storage and Light Sensitivity	Store in refrigerator at 2°C to 8°C. N.B. Refer to manufacturer PIL for specific considerations.
Patient Counseling Keys	• This drug may decrease blood cell counts. Avoid causes of bleeding and infection. • This drug may affect fertility for males or females. This may go back to normal but sometimes it may not. • This medication is a carcinogen. It may cause harm to the unborn baby. Avoid getting pregnant during administration.
Pharmaco-genomics	• Glutathione-S-Transferase Pi: Polymorphisms of the GST enzyme family may result in enhanced cytotoxicity due to altered drug metabolism.

3. Cyclophosphamide

Generic Name	Cyclophosphamide
Dosage Form/ Strengths	• Powder for injection: 200 mg, 1 gm. • Tablets: 50 mg.
Route of Administration	IV, Oral
Pharmacologic Category	Alkylating Agent (Nitrogen Mustard); Antineoplastic agent, Immunosuppressant agent, Antirheumatic agent. ATC code: L01AA01
Indications	**N.B.** Refer to literature and specific protocols for all indications. • Chronic or Acute Lymphocytic Leukemia • As preparation for a bone marrow transplantation, in the treatment of Acute Lymphoblastic Leukemia, Chronic Myelogenous Leukemia and Acute Myelogenous Leukemia, in combination with whole-body irradiation or Busulfan. • Hodgkin's lymphoma, non-Hodgkin's lymphoma, and multiple myeloma • Metastatic ovarian, and breast, carcinoma • Adjuvant treatment of breast carcinoma • Ewing's sarcoma • Small cell lung cancer • Advanced or metastatic neuroblastoma • Life-threatening autoimmune diseases: severe progressive forms of lupus nephritis and Wegener's granulomatosis. • Mycosis fungoides. • Nephrotic syndrome in pediatrics
Dosage Regimen	**N.B.** Different doses and regimens have been used; consult the literature for specific protocols. **Adult and Pediatric dosing:** **Intravenous use** **Hematologic and solid tumors** **a.** For daily treatment: 3 – 6 mg/kg body weight (= 120 – 240 mg/m^2 body surface area). **b.** For intermittent treatment: 10 – 15 mg/kg body weight (= 400 – 600 mg/m^2 body surface area), with therapy-free intervals of 2 to 5 days. **c.** For high-dose- intermittent treatment: 20 – 40 mg/kg body weight (= 800 – 1600 mg/m^2 body surface area), with therapy-free intervals of 21 to 28 days. **In preparation for a bone marrow transplantation** • IV: 60 mg/kg body weight for 2 days or 50 mg/kg for 4 days. If a Busulfan-cyclophosphamide regimen is applied, the first dose of

cyclophosphamide must be administered at least 24 hours after the last dose of Busulfan.

Autoimmune diseases

- IV: 500 – 1000 mg/m^2 monthly.

Oral dosing:

- Tumors: 100 – 300 mg daily (as a single or divided dose) **Or** 1-5 mg/kg/day. Continued until a clear remission or improvement is seen or interrupted when the leucopenia becomes unacceptable. When used in combination, a reduction of dose or extension of therapy-free interval may be needed.
- Minimal Change Nephrotic Syndrome in Pediatrics:
  Oral: 2 mg/kg daily for 8 to 12 weeks (maximum cumulative dose 168 mg per kg). Treatment beyond 90 days increases the probability of sterility in males.

Dosage Adjustment

N.B. Refer to the protocol used for specific dose modifications.

- **Altered kidney function:**
  CrCl 10 to 24 mL/minute: Monitor for signs and symptoms of toxicity.
  CrCl <10 mL/minute: Administer 50% of the normal dose.
- **Altered Hepatic function:**
  Total bilirubin 3.1– 5 mg/dl: Administer 75% of the dose.
  Total bilirubin greater than 5 mg/dL: Do not administer.
- **Adjustment for Toxicity:**
  Myelosuppression:

Leukocyte count/µl	Platelet count /µl	Dosage
> 4000	> 100 000	100% of the planned dose
2500 – 4000	50 000 – 100 000	50 % of the planned dose
< 2500	< 50 000	Discontinue until normal counts, unless essential.

Contra-Indications

- Hypersensitivity to Cyclophosphamide, any of the formulation components.
- Acute infections.
- Severe myelosuppression.
- Urinary outflow obstruction, Urinary tract infection, or Acute urothelial toxicity.
- Breastfeeding.

Adverse Drug Reactions

Bone marrow suppression and infection
Cardiotoxicity
Hemorrhagic cystitis
Hepatotoxicity
Pulmonary toxicity

	Second primary malignancy **≥10%:** Myelosuppression, Leukopenia, Neutropenia, Immunosuppression, Alopecia, Cystitis, Microhematuria, Fever. **1-10%:** Infections, Febrile neutropenia, Mucosal inflammation, Hepatic function abnormalities, Hemorrhagic cystitis, Macrohematuria, Impairment of spermatogenesis, Chills, Asthenia, Malaise.
Monitoring Parameters	• CBC with differential • Kidney function test • Monitor signs and symptoms of (hemorrhagic cystitis, urinalysis, cardiotoxicity, pulmonary toxicity, hepatic toxicity, infections) • Pregnancy test.
Drug Interactions	***Risk X: Avoid combination*** Abrocitinib, Baricitinib, BCG (Intravesical), BCG Products, Brivudine, Cladribine, Dengue Tetravalent Vaccine (Live), Deucravacitinib, Dipyrone, Etanercept, Etrasimod, Fexinidazole, Filgotinib, Mumps- Rubella- or Varicella-Containing Live Vaccines, Pimecrolimus, Poliovirus Vaccine (Live/Trivalent/Oral), Ritlecitinib, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Typhoid Vaccine, Upadacitinib Vaccines (Live), Voclosporin, Yellow Fever Vaccine. ***Risk D: Consider therapy modification*** Coccidioides immitis Skin Test, COVID-19 Vaccines, Deferiprone, Denosumab, Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Succinylcholine Vaccines (Inactivated/Non-Replicating). **Notes:** • Substances that delay the activation of cyclophosphamide include: Aprepitant, Bupropion, Busulfan, Ciprofloxacin, Chloramphenicol, Azole-antimycotics, CYP2B6 and CYP3A4 inhibitors, Prasugrel, Sulfonamides, Ondansetron, Grapefruit. • An increase in the concentration of cytotoxic metabolites may occur with: Allopurinol, Azathioprine, Chloral hydrate, Cimetidine, Disulfiram, Glyceraldehyde, Protease inhibitors, Inducers of cytochrome P450 enzymes (e.g. rifampin, phenobarbital, carbamazepine, phenytoin, St. John's wort, benzodiazepines, and corticosteroids), Dabrafenib. • Increased myelosuppression may occur with: ACE inhibitors, Natalizumab, Paclitaxel, Thiazide diuretics, Zidovudine, Clozapine • Increased cardiotoxicity may occur with: Anthracyclines, Cytarabine, Mitomycin, Pentostatin, Radiation therapy of the cardiac region, Trastuzumab

	• Increased pulmonary toxicity may result from a combined effect of cyclophosphamide and, for example: Amiodarone, G-CSF (granulocyte colony-stimulating factor). • Increased nephrotoxicity may result from a combined effect of cyclophosphamide and, for example: Amphotericin B, Indomethacin. • Increase in other toxicities: - Azathioprine: Increased risk of hepatotoxicity (liver necrosis) - Busulfan: Increased incidence of hepatic veno-occlusive disease and mucositis has been reported. - Protease inhibitors: Increased incidence of mucositis - Digoxin: Impaired absorption of digoxin during a concomitant cytotoxic treatment - Etanercept: In patients with Wegener's granulomatosis, the addition of Etanercept to standard treatment, including cyclophosphamide, was associated with a higher incidence of non-cutaneous malignant solid tumors. - Metronidazole: Acute encephalopathy has been reported in a patient receiving Cyclophosphamide and Metronidazole. - Tamoxifen: Concomitant use of Tamoxifen and chemotherapy may increase the risk of thromboembolic complications. - Coumarins: Both increased and decreased Warfarin effects have been reported in patients receiving Warfarin and Cyclophosphamide. - Depolarizing muscle relaxants: Cyclophosphamide treatment causes a marked and persistent inhibition of cholinesterase activity. - Verapamil: Impaired intestinal absorption of orally administered Verapamil.
Pregnancy and Lactation	**Pregnancy:** There is positive evidence of human fetal risk in particularly during the first trimester. Women and men should use effective methods of contraception during these periods and after 6-12 months of discontinuation. The potential benefit of the treatment should be weighed against the potential risk for the fetus. **Lactation**: Contraindicated. Should be terminated before initiating Cyclophosphamide therapy as this drug can cause toxicities to infants.
Administration	**Hazardous agent (NIOSH 2016 [group 1]):** IARC Group 1 carcinogen (Carcinogenic to Humans); harmful to the fetus during Pregnancy. Wear gloves when handling tablets; if contact occurs, wash hands immediately and thoroughly. **Administration: IV** • Intravenous infusion is preferred over direct injection. • **Duration of the infusion** should be appropriate for the volume and type of carrier fluid to be infused. To reduce the likelihood of rate-dependent adverse reactions (e.g., facial swelling, headache, nasal congestion, scalp burning), Cyclophosphamide should be injected or infused very slowly. • **Infusion rate:** refer to specific protocol; usually over 30 to 60 minutes; larger

	doses (>1,800 mg/m^2) have been infused over 1 to 6 hours by some centers and protocols. • Most adult patients will require a fluid intake of at least 2 L/day. • High-dose regimens should be accompanied by vigorous hydration with or without Mesna therapy. • Morning administration may be preferred to ensure adequate hydration throughout the day. **Preparation for administration:** **Infusion**: Reconstitute the vial by adding sterile water for injection or 0.9% sterile sodium chloride solution. Reconstituted Cyclophosphamide should be further diluted in 5% dextrose or 0.9% sodium chloride solution before infusion. **Administration: Oral** • Swallow whole; do not crush or chew. • To minimize bladder toxicity, increase normal fluid intake. • Morning administration may be preferred to ensure adequate hydration throughout the day; do not administer at bedtime. **N.B** Refer to product PIL if there are specific considerations.
Emetogenicity	**IV**: • ≥1,500 mg/m^2: High (>90%) • <1,500 mg/m^2: Moderate (30% to 90%) • **Oral**: • ≥100 mg/m^2/day Moderate or high (≥30%) • <100 mg/m^2/day Minimal to low emetic risk (<30%)
Warnings/ Precautions	**Myelosuppression, Immunosuppression, Bone Marrow Failure and Infections:** • Cyclophosphamide can cause myelosuppression (leukopenia, neutropenia, thrombocytopenia, and anemia) which may lead to serious (and fatal) infections, including sepsis and septic shock, or reactive latent infections. • The nadirs of the reduction in leukocyte and thrombocyte count are usually in 1 – 2 weeks of treatment. The bone marrow recovers after approximately 20 days. • Antimicrobial prophylaxis may be indicated in certain cases of neutropenia at the discretion of the managing physician. In the case of neutropenic fever, antibiotic therapy is indicated. Antimycotics and/or antivirals may also be indicated. **Urinary Tract and Renal Toxicity:** • Hemorrhagic cystitis, pyelitis, ureteritis, and hematuria have been reported with short-term and long-term use of Cyclophosphamide. Bladder ulceration, necrosis, or fibrosis may develop. Cystectomy may become necessary due to fibrosis, bleeding, or secondary malignancy. Cyclophosphamide has also been associated with nephrotoxicity, including renal tubular necrosis. Hyponatremia

associated with increased total body water and fatalities have occurred.

- Hematuria usually resolves in a few days after cyclophosphamide treatment is stopped, but it may persist. Severe hemorrhagic cystitis usually requires a discontinuation of the treatment with cyclophosphamide.
- Strong hydration and Mesna to force diuresis can reduce the frequency and severity of bladder toxicity.

Cardiotoxicity:

- Cardiotoxicities reported include arrhythmias, heart failure, heart block, myocarditis (including fatal hemorrhagic), pericarditis, and pericardial effusion.
- Acute cardiac toxicity has been reported with single doses as low as 20 mg/kg of cyclophosphamide.
- The risk of cardiotoxicity may be increased with high doses of cyclophosphamide, in the elderly, and patients with previous radiation treatment to the cardiac region and/or previous or concomitant treatment with other cardiotoxic agents.
- Monitor patients with risk factors for cardiotoxicity and with pre-existing cardiac disease.

Pulmonary Toxicity:

- Pulmonary toxicity leading to respiratory failure has been reported during and following treatment with cyclophosphamide. Pneumonitis may develop years after treatment with cyclophosphamide.
- While the incidence of cyclophosphamide-associated pulmonary toxicity is low, prognosis for affected patients is poor.
- Monitor patients for signs and symptoms of pulmonary toxicity.

Secondary Malignancies:

- Secondary malignancies (urinary tract cancer, myelodysplasia, acute leukemias, lymphomas, thyroid cancer, and sarcomas) have been reported in patients treated with cyclophosphamide-containing regimens.
- The risk of bladder cancer can be markedly reduced by hemorrhagic cystitis prophylaxis.

Veno-occlusive Liver Disease:

- Characterized by sudden weight gain, painful hepatomegaly, ascites, and hyperbilirubinemia/jaundice.
- A major risk factor is the cytoreductive regimen in preparation for bone marrow transplantation that consists of Cyclophosphamide in combination with whole-body irradiation, Busulfan, or other agents. VOLD has also developed gradually in patients receiving long-term low-dose immunosuppressive doses of Cyclophosphamide.
- Other risk factors include pre-existing disturbances of hepatic function, previous radiation therapy of the abdomen, and a low-performance score.
- VOLD incidence is reduced when a time interval of at least 24 hours is observed between the last administration of Busulfan and the first administration of Cyclophosphamide.

	Genotoxicity and Infertility: • Cyclophosphamide is genotoxic and mutagenic. Also, it may cause sterility in both sexes. • Women should not get pregnant during treatment and for 12 months after discontinuation of therapy. Men should not father a child during the treatment and for 6 months after discontinuation of therapy. **Impairment of Wound Healing** • **Alopecia:** Hair can be expected to grow back after treatment or even during continued treatment, though it may be different in texture or color. • **Caution in patients:** with diabetes mellitus (due to interaction with hypoglycemics), Adrenalectomized patients, patients who have recently undergone surgery (not to administer if less than 10 days ago), and hepatic or renal impairment patients.
Storage and Light Sensitivity	**Injection**: • Store intact vials of powder at ≤25°C. • Protect from light. • Reconstituted solutions in NS are stable for 24 hours at 2°C to 8°C. **Tablets**: • Store at 15°C and 30°C. Protect from light. **N.B** Refer to product PIL if there are specific considerations.
Patient Counselling Keys	• Tell your doctor if you are taking any other drugs, as your dose may need to be changed. • Your doctor may tell you to drink plenty of liquids e.g. (2-3 L a day) and to empty your bladder every 2 hours for at least 24 hours after your dose. • Side effects include nausea, vomiting, stomatitis, impaired wound healing, amenorrhea, premature menopause, sterility, and hair loss. • Take your dose early in the day (preferably no later than 3:00 pm). If you are taking one dose daily, take it at breakfast. • This medication may cause myelosuppression, immunosuppression, and infections. Avoid causes of infections and bleeding. Do your routine blood cell counts as instructed. • Tell your doctor immediately if any urinary symptoms (including a change in urine color to pink or red), cardiotoxicity symptoms (shortness of breath, cough, edema, palpitations, weight gain or dizziness, or loss of consciousness), infections, or respiratory symptoms.
Sequence of Administration	• Cell cycle phase nonspecific agent. • Nonvesicant**.** • When combined with Paclitaxel, Cyclophosphamide should be administered first for less cytopenia. • When combined with Docetaxel, Doxorubicin, or Fluorouracil, Cyclophosphamide should be administered second.

4. Ifosfamide

Generic Name	Ifosfamide
Dosage Form/Strengths	Powder for solution for I.V. Injection or infusion: 1gm, 2gm
Route of Administration	IV
Pharmacologic Category	Antineoplastic Agent, Alkylating Agent (Nitrogen Mustard) ATC: L01AA06
Indications	**N.B.** *Refer to literature and specific protocols for all indications.* • Used as a single agent or in combination with other agents to treat a wide variety of malignancies in children and adults, including soft tissue sarcoma, osteosarcoma, non-Hodgkin lymphoma, ovarian cancer, small cell bronchial cancer, non-small cell bronchial cancer Hodgkin's lymphoma, cervical cancer, metastatic breast cancer, ENT region cancer, and acute lymphoblastic leukemia. • Treatment (third line) of germ cell testicular cancer (in combination with other chemotherapy drugs) **N.B.** Should be used concurrently with mesna for prophylaxis of hemorrhagic cystitis.
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols.* **Dosing Adults:** As part of combination chemotherapy and with mesna: • IV: 1,200 mg/m^2/day for 5 days every 3 weeks or after hematologic recovery, for 4 cycles. • IV: 8-12 g/m^2 equally divided into single daily doses over 3 - 5 days every 2 - 4 weeks. **N.B.** Extensive hydration consisting of 2-4 liters of oral or intravenous fluid per day is recommended to prevent bladder toxicity. **Dosing Pediatrics:** As part of combination chemotherapy and with mesna: • IV:5 g/m^2 over 24 hours. • IV: 9 g/m^2 equally fractionated as single daily doses over 5 days. • IV: 9 g/m^2 as a continuous infusion over 72 hours- repeated at three weekly intervals. **Note:** Uroprotection with mesna is mandatory during ifosfamide administration:

	Where Ifosfamide is used as an IV short infusion: Mesna is given in a dosage equal to 20% of the Ifosfamide on 0, 4, 8 hours over 15-30 minutes (Total dose = 160% (w/w) of the Ifosfamide dose). **Where Ifosfamide is used as a 24-hour infusion:** Mesna can be used as a concurrent infusion. An initial 20% (w/w) of the total Ifosfamide dose is given as an IV bolus, then an infusion of 100% (w/w) of the Ifosfamide over 24 hours, followed by a further 12-hour infusion of 60% (w/w) of the Ifosfamide dose. Total Mesna dose = 180% of the Ifosfamide dose. **N.B.** extensive hydration consisting of at least 2 liters of oral or intravenous fluid per day to prevent bladder toxicity.
Dosage Adjustment	**N.B.** *Refer to the protocol used for specific dose modifications.* **Dosing: Altered Kidney Function: Adult and pediatric:** Consider dose adjustment and reduction in patients with kidney dysfunction. The following dosing adjustments have been used according to the literature: CrCl 46 to 60 mL/minute: Administer 80% of the dose. CrCl 31 to 45 mL/minute: Administer 75% of the dose. CrCl <30 mL/minute: Administer 70% of the dose. **Dosing: Hepatic Impairment: Adult and pediatric:** - Mild or moderate impairment: No dosage adjustment necessary. - Severe impairment: Use is not recommended. **Dosing: Adjustment for Toxicity: Adult** - WBC <2,000/mm^3 and/or platelets <50,000/mm^3: Avoid administering Ifosfamide (unless clinically necessary). - Antimicrobial prophylaxis may be necessary in some neutropenic patients; administer antibiotics and/or antifungal agents for neutropenic fever. - Encephalopathy: Discontinue Ifosfamide. Methylene blue may be used for the treatment and prophylaxis of ifosfamide-associated encephalopathy. - Microscopic hematuria (detected via urinalysis): Withhold Ifosfamide until complete resolution.
Contra-Indications	• Known hypersensitivity to administration of Ifosfamide. • Bladder obstruction • Urinary tract obstruction • Severe myelosuppression. • Severe renal or hepatic impairment
Adverse Drug Reactions	Neurotoxicity, encephalopathy Nephrotoxicity Myelosuppression **>10%**

	Dermatologic: Alopecia (90%). **Gastrointestinal**: Nausea and vomiting (47%) **Genitourinary**: Gross hematuria (11%; with mesna: 5%), hematuria (44%; with mesna: 21%). **Hematologic & oncologic:** Bone marrow depression (including anemia [38%], granulocytopenia, leukopenia [grade 4: 44%], lymphocytopenia, neutropenia, pancytopenia, and thrombocytopenia [5%]). **Nervous system**: Central nervous system toxicity (≤15%; including neurotoxicity: abnormal electroencephalogram, aphasia, ataxia, cerebellar syndrome, coma, cranial nerve disorder, encephalopathy, extrapyramidal reaction, hallucination, impaired consciousness, motor dysfunction, muscle spasm, myoclonus, peripheral neuropathy [<1%], psychotic reaction, seizure, tremor). **1% to 10%** **Gastrointestinal**: Anorexia (1%). **Hematologic & oncologic:** Febrile neutropenia (1%). **Hepatic**: Hepatotoxicity (2% including hepatorenal syndrome, increased gamma-glutamyl transferase, increased lactate dehydrogenase, increased serum alanine aminotransferase, increased serum alkaline phosphatase, increased serum aspartate aminotransferase, increased serum bilirubin, jaundice). **Infection**: Infection (10%; including bacterial infection, fungal infection, infection due to an organism in genus *Pneumocystis*, parasitic infection [*Strongyloides* infection], pneumonia, reactivation of disease [latent infections], sepsis, septic shock, and viral infection [herpes zoster infection]). **Local**: Localized phlebitis (3%).
Monitoring Parameters	• CBC with differential • Liver and Kidney functions • Urine output and urine analysis. • Monitor serum and urine chemistries including phosphorus and potassium regularly. • Monitor for signs/symptoms of neurotoxicity, pulmonary toxicity, urotoxicity/hemorrhagic cystitis, and secondary malignancies.
Drug Interactions	***Risk X: Avoid combination*** Abrocitinib, Baricitinib, BCG (Intravesical), BCG Products, Brivudine, Cladribine, Dengue Tetravalent Vaccine (Live), Deucravacitinib, Dipyrone, Fexinidazole, Fusidic Acid (Systemic), Mumps- Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Poliovirus Vaccine (Live/Trivalent/Oral), Ritlecitinib, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Typhoid Vaccine, Upadacitinib, Vaccines (Live), Yellow Fever Vaccine. ***Risk D: Consider therapy modification***

	Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), Deferiprone, Denosumab, Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating).
Pregnancy and Lactation	**Pregnancy:** Avoid particularly in the first trimester. Fetal growth retardation and neonatal malformations occurred. Patients treated with Ifosfamide should take contraceptive measures after discontinuation of therapy for at least 1 year for women and 6 months for men. Fertility may occur in men or women. **Lactation:** Not recommended during Ifosfamide treatment; due to the potential for serious adverse reactions.
Administration	• To prevent bladder toxicity, should be given with mesna and extensive hydration consisting of at least 2 liters of oral or intravenous fluid per day. **Preparation for Administration: Adult** Add 25 ml of Water for Injections. The solution may be: - Diluted to less than a 4% solution in NS 0.9% and injected directly into the vein, with the patient supine. - Infused in NS 0.9% over 30-120 mins. - Injected directly into a fast-running infusion. - Made up of 3 litres of NS 0.9% and infused over 24 hours. Each liter should be given over eight hours. **Hazardous agent** (NIOSH 2016 [group 1]). Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. N.B. Refer to manufacturer PIL for specific considerations.
Emetogenicity	• Ifosfamide ≥2 g/m^2 per dose: High emetic risk (>90% frequency of emesis). • Ifosfamide <2 g/m^2 per dose: Moderate emetic risk (>30%–90% frequency of emesis).
Warnings/ Precautions	**Myelosuppression**: Ifosfamide-induced myelosuppression can cause leukopenia, neutropenia, and thrombocytopenia. The nadir of the leukocyte counts may be approximately during the second week after administration. The use of a hematopoiesis-stimulating agent may be considered. Myelosuppression can be severe and lead to fatal infections. Close hematologic monitoring is recommended. **CNS toxicity:** May be severe and result in encephalopathy and death. Monitor for CNS toxicity and discontinue treatment for encephalopathy. Neurotoxicity may occur within a few hours to a few days after first administration and in most cases resolves within 48 to 72 hours of Ifosfamide discontinuation. **Hemorrhagic cystitis**: Hemorrhagic cystitis can be severe and can be reduced by the prophylactic use of mesna.

	Nephrotoxicity: Nephrotoxicity can be severe and result in renal failure. **Cardiotoxicity:** The risk of developing cardiotoxic effects is dose-dependent. It is increased in patients with prior or concomitant treatment with other cardiotoxic agents or radiation of the cardiac region and, possibly, renal impairment. Fatal cardiotoxicity has been reported. Particular caution should be exercised when Ifosfamide is used in patients with risk factors for cardiotoxicity and in patients with preexisting cardiac disease. **Pulmonary Toxicity:** Interstitial pneumonitis, pulmonary fibrosis, and other forms of pulmonary toxicity have been reported with Ifosfamide treatment. Monitor for signs and symptoms of pulmonary toxicity and treat as clinically indicated. **Anaphylactic Reactions:** Anaphylactic reactions have been reported in association with Ifosfamide. **Secondary Malignancies:** Malignancies reported after the use of ifosfamide or regimens with ifosfamide include lymphoma, thyroid cancer, and sarcomas.
Storage and Light Sensitivity	• Store at 15°C to 30°C. • After dilution Chemical and physical in-use stability has been demonstrated for 17 hours at 25°C in Sodium Chloride 0.9% or for 24 hours if refrigerated. N.B. Refer to manufacturer PIL for specific considerations.
Patient Counseling Keys	• This drug induces low blood cell counts. Avoid infections and bleeding causes. • Follow your lab tests as instructed by the doctor. • Call your doctor if you develop any symptoms of nervous system, pulmonary, or kidney disorders. • Hydration (2-4 liters) is essential during treatment with this medicine to prevent severe adverse effects. • This drug is carcinogenic and teratogenic. Avoid pregnancy and lactation during use.
Sequence of Administration	• Cell cycle-phase nonspecific. • Irritant. • When combined with Paclitaxel, Ifosfamide may be given first for less toxicity. • When combined with Docetaxel, Ifosfamide should be given first for less toxicity

5. Melphalan

Generic Name	Melphalan
Dosage Form/ Strengths	Tablet: 2 mg.
Route of Administration	Oral.
Pharmacologic Category	Antineoplastic Agent, Alkylating Agent (Nitrogen Mustard). ATC code: L01AA03
Indications	**N.B.** *Refer to literature and specific protocols for all indications*. • Multiple myeloma. • Advanced ovarian cancer. • Polycythemia rubra vera. • Advanced breast cancer.
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols.* **Adult dosing**: • **Multiple myeloma**: Note: Administration of Melphalan and Prednisone is more effective than Melphalan alone. **Different regimens are used:** - **Oral**: 0.15-0.25 mg/kg/day in divided doses for 4 days. Repeat at intervals of six weeks. - **Oral:** 6mg daily for 2-3 weeks (adjust the dose if needed on weekly blood count results) then rest period for up to 4 weeks. When white blood cell and platelet counts are rising, use a maintenance dose of 2 mg daily. - **Oral**: 10 mg/day for 7 to 10 days. Continuous maintenance therapy: 2 mg/day is instituted when the white blood cell count is greater than 4,000 cells/mcL and the platelet count is greater than 100,000 cells/mcL. - **Oral**: 0.15 mg/kg/day for 7 days. Rest period 2-6 weeks. The maintenance dose is 0.05 mg/kg/day or less and is adjusted according to the blood count. • **Ovarian cancer**: **Oral**: 0.2 mg/kg/day for 5 days, repeat every 4 to 8 weeks or as soon as the bone marrow has recovered • **Advanced breast cancer**: **Oral**: 0.15 mg/kg/day (or 6 mg/m^2) for 5 days, repeated every 6 weeks. • **Polycythemia rubra vera**: **Oral**: 6 to 10 mg daily for 5 to 7 days, then will be reduced to 2 to 4 mg daily until satisfactory disease control is achieved. Therapy is maintained with a dose of 2-6 mg per week.

	Pediatrics: Effectiveness and safety in pediatrics have not been established.
Dosage Adjustment	**N.B.** *Refer to the protocol used for specific dose modifications.* • **Dosing: Altered Kidney Function: Adult** Oral: Moderate to severe renal impairment: Consider a reduced dose initially. • **Dosing: Hepatic Impairment: Adult** Oral: Melphalan is hepatically metabolized; however, dosage adjustment does not appear to be necessary.
Contra-Indications	• History of severe hypersensitivity to Melphalan.
Adverse Drug Reactions	**>10%** **Cardiovascular**: Peripheral edema (33%). **Endocrine & metabolic**: Hypokalemia (74%), hypophosphatemia (49%) **Gastrointestinal**: Abdominal pain (28%), constipation (48%), decreased appetite (49%), diarrhea (93%), dysgeusia (28%), dyspepsia (26%), nausea (90%), stomatitis (28% to 38%; grades 3/4: 5% to 13%), vomiting (64%). **Hematologic & oncologic**: Anemia (≥50%), decreased neutrophils (≥50%), decreased platelet count (≥50%), decreased white blood cell count (≥50%), febrile neutropenia (41%; grades 3/4: 28%), lymphocytopenia (≥50%). **Nervous system**: Dizziness (38%), fatigue (77%) **Miscellaneous**: Fever (48%). **1% to 10%** **Genitourinary**: Amenorrhea (9%). **Hypersensitivity**: Anaphylaxis (≤2%), hypersensitivity reaction (≤2%). **Post-marketing:** **Cardiovascular**: Vasculitis. **Dermatologic**: Allergic skin reaction, alopecia, maculopapular rash, skin necrosis, skin ulceration at the injection site. **Hematologic and oncologic**: Acute leukemia, carcinoma, hemolytic anemia, myelodysplastic syndrome. **Hepatic**: Abnormal hepatic function tests, hepatic sinusoidal obstruction syndrome, hepatitis, jaundice. **Nervous system:** Flushing sensation, tingling sensation. **Respiratory**: Interstitial pneumonitis, pulmonary fibrosis.
Monitoring Parameters	• CBC with differential platelet count, and hemoglobin. • Renal function test.

Drug Interactions	***Risk X: Avoid combination:*** Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, Dengue Tetravalent Vaccine (Live), Deucravacitinib, Dipyrone, Etrasimod, Fexinidazole, Filgotinib, Mumps- Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Poliovirus Vaccine (Live/Trivalent/Oral), Ritlecitinib, uxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Typhoid Vaccine, Upadacitinib, Vaccines (Live), Yellow Fever Vaccine. ***Risk D: Consider therapy modification*** Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), Deferiprone, Denosumab, Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T Immunosuppressants, Vaccines (Inactivated/Non-Replicating).
Pregnancy and Lactation	**Pregnancy:** Melphalan can cause fetal harm when administered to a pregnant woman. **Lactation**: Not recommended due to the potential for serious adverse reactions in the breastfed infant.
Administration	**Hazardous agen**t (NIOSH 2016 [group 1]): Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. **Oral:** Administer on an empty stomach. **N.B**. Refer to manufacturer PIL for specific considerations.
Warnings/ Precautions	**Bone marrow suppression:** • Severe bone marrow suppression can lead to infection or bleeding. • Use with caution in patients with prior bone marrow suppression, impaired renal function (consider dose reduction), or who have received prior (or concurrent) chemotherapy or irradiation. **GI toxicity:** • GI toxicities, including nausea, vomiting, diarrhea, and mucositis are common, particularly when used in high doses for conditioning regimens • Nutritional support and/or analgesics may be necessary in patients with severe mucositis. **Secondary malignancy:** • Melphalan is considered potentially leukemogenic in humans. • Secondary malignancies (including acute myeloid leukemia, myeloproliferative disease, and carcinoma) have been reported (some patients were receiving combination chemotherapy or radiation therapy);

	the risk is increased with increased treatment duration and cumulative doses.
Emetogenicity	Oral: Minimal or low (<30%).
Storage and Light Sensitivity	**Oral Melphalan:** • Store at 2°C to 8°C. • Protect from light. **N.B**. Refer to manufacturer PIL for specific considerations.
Patient Counseling Keys	• Take melphalan on an empty stomach, with a full glass of water, at the same time each day. If this upsets your stomach, you may take melphalan with food and tell your doctor. • This medicine affects blood counts. Avoid causes of infection and bleeding. • A blood test may be taken before each treatment. The dose and timing of your chemotherapy may be changed based on the test results and/or other side effects. • You may be given a prescription for antiemetics to take before your chemotherapy treatment. • Talk with your doctor before getting any vaccines.
Pharmaco -genomics	**Glutathione-S-Transferase Pi (GSTP1).** • **May Alter Pharmacodynamics** Polymorphisms of the GST enzyme family may result in enhanced cytotoxicity due to altered drug metabolism and reduced detoxification.

C. Nitrosoureas

1. Lomustine

Generic Name	Lomustine
Dosage Form/Strengths	Capsule: 40 mg.
Route of Administration	Oral.
Pharmacologic Category	Antineoplastic Agent, Alkylating Agent (Nitrosourea). ATC code: L01AD02
Indications	**N.B.** *Refer to literature and specific protocols for all indications.* • Brain tumors (primary or metastatic). • Lung tumors (especially oat-cell carcinoma). • Hodgkin's disease (resistant to conventional combination chemotherapy). • Malignant melanoma (metastatic). **Other indications**: as a second line for non-Hodgkin's lymphoma, myelomatosis, gastrointestinal tumors, carcinoma of the kidney, the testis, the ovary, the cervix uteri, and the breast
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols*. **Dosing adult and pediatric**: **Oral**: • Single agent: 120 – 130 mg/m² as a single dose every 6 to 8 weeks (or as a divided dose over 3 days, e.g. 40 mg/m²/day). • In combination with other chemotherapeutic agents: Dosage is reduced. Avoid cumulative dose >1000mg/m^2.
Dosage Adjustment	**N.B.** *Refer to the protocol used for specific dose modifications.* • **Dosage adjustment in hematological toxicities:**

Nadir After Prior Dose		Dose Adjustment
Leukocytes (/mm3)	**Platelets (/mm³)**	
2000 – 2999	25,000 – 74,999	Reduce dose by 70%
< 2000	< 25,000	Reduce dose by 50%

	• **Dosing: Altered Kidney Function:** No specific recommendations for dose adjustments. Contraindicated in severe renal impairment. • **Dosing: Hepatic Impairment:** No specific recommendations for dose adjustments.
Contra-Indications	• Hypersensitivity to the active substance(s) or any of the excipients. • Previous hypersensitivity to nitrosoureas. • Previous failure of the tumor to respond to other nitrosoureas. • Severe bone marrow depression. • Severe renal impairment. • Coeliac disease or wheat allergy. • Concomitant use of yellow fever vaccine or other live vaccines. • Pregnancy and breastfeeding.
Adverse Drug Reactions	• **Dermatologic**: Alopecia. • **Gastrointestinal**: Nausea, stomatitis, vomiting and anorexia. • **Hematologic & oncologic**: Bone marrow depression, leukopenia, second primary malignant neoplasm (including acute leukemia and myelodysplastic syndrome), thrombocytopenia. • **Hepatic**: Hepatotoxicity, increased serum alkaline phosphatase, increased serum bilirubin, increased serum transaminases. • **Nervous system**: Ataxia, disorientation, dysarthria, lethargy. • **Ophthalmic**: Blindness, optic atrophy, visual disturbance. • **Renal**: Nephron atrophy, renal failure syndrome. • **Respiratory**: Pulmonary infiltrates.
Monitoring Parameters	• CBC with differential platelet count, and hemoglobin (weekly for at least 6 weeks after a dose). • Liver function test. • Renal function test. • Monitor for secondary malignancies.
Drug Interactions	***Risk X: Avoid combination:*** Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, Dengue Tetravalent Vaccine (Live), Deucravacitinib, Dipyrone, Etrasimod, Fexinidazole, Filgotinib, Mumps- Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Poliovirus Vaccine (Live/Trivalent/Oral), Ritlecitinib, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Typhoid Vaccine, Upadacitinib, Vaccines (Live), Yellow Fever Vaccine. ***Risk D: Consider therapy modification*** Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), Deferiprone, Denosumab, Influenza Virus

	Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating).
Pregnancy and Lactation	**Pregnancy:** Avoid use during pregnancy. Birth defects may occur. Men and women are recommended to take contraceptive precautions during therapy with Lomustine and for 6 months after treatment. Irreversible infertility risk for men. **Lactation**: Lomustine is contraindicated during breastfeeding. Due to the lipophilic nature of lomustine, it is likely to be excreted in human milk.
Administration	**Hazardous agent (NIOSH 2016 [group 1]):** Carcinogenic. Use appropriate precautions for receiving handling, storage, preparation, dispensing, transporting, administration, and disposal. **Administration: Oral** • Administering on an empty stomach may reduce the incidence of nausea and vomiting. • Do not break capsules. If contact with skin occurs, immediately wash the area thoroughly; avoid exposure to broken capsules. • Antiemetics are recommended to prevent nausea and vomiting. **N.B**. Refer to manufacturer PIL for specific considerations.
Emetogenicity	Moderate to high emetic risk (≥30% frequency of emesis).
Warnings/ Precautions	**Delayed bone marrow suppression:** Lomustine causes cumulative myelosuppression, which may result in fatal infections or bleeding. Hematologic toxicity is dose-related and delayed (occurring 4 to 6 weeks after drug administration and persisting for 1 to 2 weeks). Do not administer Lomustine more frequently than once every 6 weeks. **Hepatotoxicity:** Hepatotoxicity (transaminase, alkaline phosphatase, and bilirubin elevations) has been reported. **Pulmonary toxicity:** May cause dose-related pulmonary toxicity (infiltrates and/or fibrosis). Pulmonary toxicity is usually related to cumulative doses >1,100 mg/m^2. May be delayed 6 months or longer after treatment initiation. Perform pulmonary function tests before treatment and repeat frequently. Permanently discontinue in patients diagnosed with pulmonary fibrosis. **Renal toxicity and liver dysfunction:** Progressive renal failure or hepatotoxicity has been reported after treatment. Use with caution; monitor periodically. **Secondary malignancies:** Long-term use of nitrosoureas is associated with the development of secondary malignancies, including acute leukemia and myelodysplasia. **Cross-resistance** with other nitrosoureas is usual, but cross-resistance with conventional alkylating agents is unusual.

	• **Overdosage:** symptoms include severe myelosuppression, as well as abdominal pain, diarrhea, vomiting, anorexia, lethargy, dizziness, abnormal hepatic function, cough, and shortness of breath. Treat immediately by gastric lavage and supportive treatment.
Storage and Light Sensitivity	• Store between 15°C and 30°C. • Store in the original container to protect from light and moisture. **N.B**. Refer to manufacturer PIL for specific considerations.
Patient Counseling Keys	• This medicine may affect blood counts. Avoid causes of infection and bleeding. • This medicine is carcinogenic and teratogenic. Caution with handling. Use contraception during use. Risk of irreversibly reduced fertility. • Have your blood and lung functions checked as you have been told by your doctor. • Talk with your doctor before getting any vaccines. • Tell your doctor if you are allergic to this drug or any other drugs. • Taking this drug on an empty stomach may help prevent an upset stomach or throwing up. Talk with the doctor.

2. Temozolomide

Generic name	Temozolomide
Dosage Form/ Strengths	Capsules 5mg, 20mg, 100mg, 250mg
Route of Administration	Oral
Pharmacologic Category	Antineoplastic Agent, Alkylating Agent ATC: L01AX03
Indications	**N.B.** *Refer to literature and specific protocols for all indications*. • In adults with newly diagnosed glioblastoma multiforme (an aggressive type of brain tumor). Used first with radiotherapy and then on its own. • Malignant gliomas such as glioblastoma multiforme or anaplastic astrocytoma when the tumor has returned or got worse after standard treatment. ***Other indications:*** Melanoma (Cutaneous), soft tissue sarcoma
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols.* • **Newly Diagnosed Glioblastoma**: 75 mg/m^2 once daily for 42 days concomitant with focal radiotherapy followed by an initial maintenance dose of 150 mg/m^2 once daily for Days 1 to 5 of each 28-day cycle for 6 cycles. May increase maintenance dose to 200 mg/ m^2 for cycles 2 – 6 based on toxicity. Provide Pneumocystis pneumonia (PCP) prophylaxis during the concomitant phase and continue in patients who develop lymphopenia until resolution to grade 1 or less. • **Refractory Anaplastic Astrocytoma**: Initial dose of 150 mg/m^2 once daily on Days 1 to 5 of each 28-day cycle.
Dosage Adjustment	**N.B.** *Refer to the protocol used for specific dose modifications*. ***Dosing: Altered Kidney Function: Adult*** CrCl ≥36 mL/minute/m ^{2}: No dosage adjustment necessary. CrCl <36 mL/minute/m ^{2}: There are no dosage adjustments available (has not been studied). Dialysis patients: There are no dosage adjustments available (has not been studied). ***Dosage: Hepatic Impairment: Adult*** Mild to moderate impairment (Child-Pugh classes A and B): No dosage adjustment necessary. Severe impairment (Child-Pugh class C): There are no dosage adjustments available (has not been studied).
Contra-indications	• Hypersensitivity to Temozolomide or any component of the formulation. • Hypersensitivity to dacarbazine (both drugs are metabolized to [methyl-triazene-1-yl]-imidazole-4-carboxamide).

	• Not recommended in patients with severe myelosuppression.
Adverse Drug Reactions	**>10%** **Cardiovascular**: Peripheral edema (11%). **Dermatologic**: Alopecia (55%), skin rash (8% to 13%). **Gastrointestinal**: Nausea (49% to 53%), vomiting (29% to 42%), constipation (22% to 33%), anorexia (9% to 27%), diarrhea (10% to 16%). **Hematologic & oncologic**: Lymphocytopenia (grades 3/4: 55%), thrombocytopenia (8%; grades 3/4: 4% to 19%), decreased neutrophils (grades 3/4: 14%), leukopenia (grades 3/4: eleven%). **Infection**: Viral infection (11%). **Nervous system**: Fatigue (34% to 61%), headache (23% to 41%), seizure (6% to 23%), hemiparesis (18%), dizziness (5% to 12%), ataxia (8% to eleven%). **Neuromuscular & skeletal**: Asthenia (7% to 13%). **Miscellaneous**: Fever (13%). **1% to 10%** **Dermatologic**: Pruritus (5% to 8%), xeroderma (5%), erythema of skin (1%). **Endocrine & metabolic**: Hypercorticoidism (8%), weight gain (5%). **Gastrointestinal**: Stomatitis (9%; grades ≥3: 1%), abdominal pain (5% to 9%), dysphagia (7%), dysgeusia (5%). **Genitourinary**: Urinary incontinence (8%), urinary tract infection (8%), mastalgia (females: 6%), urinary frequency (6%). **Hematologic & oncologic**: Decreased hemoglobin (grades 3/4: 4%). **Hypersensitivity**: Hypersensitivity reaction (3%). **Nervous system**: Amnesia (10%), insomnia (4% to 10%), drowsiness (9%), paresthesia (9%), paresis (8%), anxiety (7%), memory impairment (7%), abnormal gait (6%), depression (6%), confusion (5%). **Neuromuscular & skeletal**: Back pain (8%), arthralgia (6%), myalgia (5%). **Ophthalmic**: Blurred vision (5% to 8%), diplopia (5%), visual disturbance (visual deficit/vision changes: 5%). **Respiratory**: Pharyngitis (8%), upper respiratory tract infection (8%), cough (5% to 8%), sinusitis (6%), dyspnea (5%).
Monitoring Parameters	• CBC with differential • Liver function test • Pregnancy testing • Hepatitis B virus (HBV) screening
Drug Interactions	***Risk X: Avoid combination*** Abrocitinib, Baricitinib, BCG Products, Brivudine, Chikungunya Vaccine (Live), Chloramphenicol (Systemic), Cladribine, Dengue Tetravalent Vaccine (Live), Deucravacitinib, Etrasimod, Fexinidazole, Filgotinib, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Poliovirus Vaccine (Live/Trivalent/Oral), Mumps- Rubella- or Varicella-Containing Live Vaccines, Ritlecitinib, Ruxolitinib

	(Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide Typhoid Vaccine, Upadacitinib Vaccines (Live), Yellow Fever Vaccine. ***Risk D: Consider therapy modification*** Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), Deferiprone, Denosumab, Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Palifermin, Pimecrolimus, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating).
Pregnancy and Lactation	**Pregnancy**: Temozolomide may cause fetal harm based on the mechanism of action and findings in animal reproduction studies. Patients of reproductive potential should be advised to use effective contraception during treatment with temozolomide and for 6 months (females) or 3 months (males) after the last dose. May impair male fertility. **Lactation**: Due to the potential for serious adverse reactions (including myelosuppression) in the breastfed infant, breastfeeding is not recommended during treatment and for at least 1 week after the last temozolomide dose.
Administration	**Hazardous agent** (NIOSH 2016 [group 1]): Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. **Administration: Oral** Swallow capsules whole with a full glass of water; do not open or chew. Administer consistently concerning food (either consistently fasting or nonfasting). Administer on an empty stomach and/or at bedtime to reduce nausea and vomiting. Do not repeat the dose if vomiting occurs after the dose is administered. **N.B.** Refer to manufacturer PIL for specific considerations.
Emetogenicity	Temozolomide is associated with a moderate or high emetic potential; Antiemetics are recommended to prevent nausea and vomiting.
Warnings/ Precautions	***Concerns related to adverse effects:*** • Bone marrow suppression: Myelosuppression (including leukopenia, anemia, and pancytopenia), some with fatal outcomes, may occur. Hematologic toxicity may require treatment interruption, dose reduction, and/or discontinuation. An increased risk of hematologic toxicity has been reported in geriatric and female patients. ANC should be ≥1,500/mm3 and platelets ≥100,000/mm3 before treatment. • Hepatotoxicity: Hepatotoxicity has been reported; may be severe or fatal. • Hypersensitivity: Allergic reactions (including anaphylaxis) have been observed with temozolomide. • *Pneumocystis* pneumonia: *Pneumocystis jirovecii* pneumonia (PCP) may occur in patients receiving temozolomide; risk is increased in those receiving corticosteroids or with longer temozolomide treatment regimens. Provide PCP prophylaxis to all patients with newly diagnosed glioblastoma receiving concomitant phase radiotherapy; continue in patients with lymphopenia until

	lymphopenia resolves to ≤ grade 1. • Secondary malignancies: Cases of myelodysplastic syndromes and secondary malignancies, including myeloid leukemia, have been reported following treatment with temozolomide. ***Disease-related concerns:*** • Hepatic impairment: Use with caution in patients with severe hepatic impairment. • Renal impairment: Use with caution in patients with severe renal impairment; has not been studied in dialysis patients. ***Special populations:*** • Older adult: Patients ≥70 years of age experienced a higher incidence of grade 4 neutropenia and thrombocytopenia in cycle 1 (compared to younger patients). ***Dosage forms specific issues:*** • Polysorbate 80: Some dosage forms may contain polysorbate 80 (also known as Tweens). Hypersensitivity reactions are usually a delayed reaction. Refer to the product insert. ***Other warnings/cautions:*** • Administration schedule: Administration schedule (intermittent versus continuous) varies based on indication. • Temozolomide resistance: Increased O-6-methylguanine-DNA methyltransferase (MGMT) activity/levels within tumor tissue is associated with temozolomide resistance.
Storage and Light Sensitivity	Oral capsule: store from 15°C to 30°C. No precautions are needed for light protection. N.B. Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• This drug induces low blood cell counts. Avoid infections and bleeding causes. • This drug is Carcinogenic, Teratogenic, and emetogenic. • Refer to the doctor in case of signs of infection, bleeding, allergic reaction, shortness of breath, seizures, and memory or vision disturbances.
Pharmaco-genomics	O-6-Methylguanine-DNA Methyltransferase (MGMT)

D. Platinum Compounds

1. Carboplatin

Generic name	Carboplatin
Dosage Form/ Strengths	Solution For I.V Infusion: 10 mg, 50mg, 150 mg, 450 mg
Route of Administration	Intravenous
Pharmacologic Category	Antineoplastic Agent, Alkylating Agent, Platinum Analog ATC: L01XA02
Indications	**N.B.** *Refer to literature and specific protocols for all indications.* • Initial and secondary treatment of advanced ovarian carcinoma in combination with Cyclophosphamide. • Small cell lung carcinoma. **Other indications**: Bladder, breast cancer, cervical cancer, endometrial cancer, gastric cancer, esophageal cancer, head and neck cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, non–small cell lung cancer, and testicular cancer.
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols.* • **Adults:** -The recommended dose: is 400 mg/m^2, for previously untreated patients with normal kidney functions, given as a single intravenous infusion over 15 to 60 minutes. **-Alternatively,** the Calvert formula may be used to determine dosage: Dose (mg)= Target AUC (mg/ml x min) x [GFR ml/min + 25]

Planned Chemotherapy	Patient Treatment status	Target AUC
Single-agent Carboplatin	Previously untreated	5-7 mg/ml.min
Single-agent Carboplatin	Previously treated	4-6 mg/ml.min
Carboplatin plus Cyclophosphamide	Previously untreated	4-6 mg/ml.min

The GFR value within the Calvert formula should not exceed 125 mL/min.
The Maximum dose of Carboplatin for AUC 4 is 600mg.
The Maximum dose of Carboplatin for AUC 5 is 750mg.
The Maximum dose of Carboplatin for AUC 6 is 900mg.

-Therapy should not be repeated until:
The neutrophil count is at least 2,000 cells/mm^3
And platelet count is at least 100,000 cells/mm^3.

	• **Pediatrics:** There is insufficient data to support dosing in pediatrics, which may be used with lower doses.
Dosage Adjustment	**N.B.** *Refer to the protocol used for specific dose modifications.* **Dose adjustments in renal impairment:** **Baseline Creatinine Clearance** / **Initial Dose (Day 1)** **41-59 ml/min** — 250 mg/m^2 I.V. **16-40 ml/min** — 200 mg/m^2 I.V. **below 15 mL/min** — Data is too limited -Subsequent doses are to be adjusted according to tolerance and hematological toxicity. **Dose adjustments in hepatic impairment:** No adjustments are required. **Patients with risk factors such as previous myelosuppressive therapy**: The initial dosage should be reduced by 20-25%, particularly in Platelets <50,000, and neutrophils <500.
Contra-Indications	• Hypersensitivity to the active substance, any of the excipients, or other Platinum-containing compounds. • Patients with severe myelosuppression. • Patients with pre-existing severe renal impairment unless benefits outweigh the risks. • Patients with bleeding tumors. • Concomitant use with yellow fever vaccine.
Adverse Drug Reactions	**Hypersensitivity:** Symptoms may vary in severity and include pruritus, rash, palmar erythema, fever, chills, rigors, swelling (face, tongue, and infusion arm), GI upset, dyspnea, wheezing, tachycardia, and hypertension or hypotension. **Bone marrow suppression:** Dose-related and may be severe; may result in infection (due to neutropenia) or bleeding (due to thrombocytopenia). Anemia (which is cumulative) may require a blood transfusion. **Nausea and vomiting:** Usually begins within 6-12 hours after administration and may persist for up to 24 hours or longer. **Neurotoxicity:** Peripheral sensory neuropathy (e.g., paresthesia) is less frequent or severe

	than with cisplatin. **>10%** **Endocrine & metabolic**: Decreased serum calcium (22% to 31%), decreased serum magnesium (29% to 43%), decreased serum potassium (20% to 28%), decreased serum sodium (29% to 47%). **Gastrointestinal**: Gastrointestinal pain (17%), nausea (10% to 15%), nausea and vomiting (92%), vomiting (65% to 81%; severe vomiting: 22%). **Hematologic & oncologic**: Anemia (21% to 90%), leukopenia (15% to 85%), neutropenia (16% to 67%), thrombocytopenia (25% to 62%). **Hepatic**: Increased serum alkaline phosphatase (24% to 37%), increased serum aspartate aminotransferase (15% to 19%). **Nervous system**: Asthenia (11%), pain (23%). **Renal**: Decreased creatinine clearance (27%), increased blood urea nitrogen (14% to 22%). **1% to 10%** **Dermatologic**: Alopecia (2% to 3%). **Gastrointestinal**: Constipation (6%), diarrhea (6%), dysgeusia (1%), stomatitis (1%). **Hematologic & oncologic**: Hemorrhage (5%; including iatrogenic bleeding) **Hepatic**: Increased serum bilirubin (5%). **Hypersensitivity**: Hypersensitivity reaction (2%). **Infection**: Infection (5%). **Nervous system**: Neurotoxicity (5%), peripheral neuropathy (4% to 6%) **Ophthalmic**: Visual disturbance (1%). **Otic**: Ototoxicity (1%). **Renal**: Increased serum creatinine (6% to 10%).
Monitoring Parameters	• CBC with differential (Before therapy and at weekly intervals thereafter) • Liver function test • Kidney function test (AST ALT, alkaline phosphatase) • Audiology evaluations (children <6 months of age)
Drug Interactions	***Risk X: Avoid combination*** Abrocitinib, Baricitinib, BCG (Intravesical), BCG Products, Brivudine, Cladribine, Dengue Tetravalent Vaccine (Live), Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Mumps- Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Natalizumab, Phenytoin, fosphenytoin, Pimecrolimus, Poliovirus Vaccine (Live/Trivalent/Oral), Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Typhoid Vaccine, Upadacitinib Vaccines (Live), Yellow Fever Vaccine.

	Risk D: Consider therapy modification Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), Deferiprone Denosumab, Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Sorafenib, Taxane Derivatives, Topotecan, Vaccines (Inactivated/Non-Replicating).
Pregnancy and Lactation	**Pregnancy:** Carboplatin is embryotoxic and teratogenic in animal models. There are no adequate and well-controlled studies in pregnant women. Patients should use effective contraception during treatment and 6 months after discontinuation. Male and female fertility may be impacted by treatment with Carboplatin which may be related to dose and length of therapy and may be irreversible. **Lactation**: Women should discontinue breastfeeding during Carboplatin therapy due to the risk of serious adverse reactions in nursing infants.
Administration	• **Hazardous Drugs (NIOSH 2016)** Use appropriate precautions for receiving handling, storage, preparation, dispensing, transporting, administration, and disposal. • **Administration: IV** - Infuse over at least 15 minutes; usually infused over 15 to 60 minutes, lengthening the duration of single intravenous administration to 24 hours or dividing the total dose over 5 consecutive daily pulse doses has resulted in reduced emesis. - Needles or IV administration sets that contain aluminum should not be used in the preparation or administration of carboplatin; aluminum can react with carboplatin resulting in precipitate formation and loss of potency. • **Extravasation management**: If extravasation occurs, stop infusion immediately and disconnect (leave cannula/needle in place); gently aspirate extravasated solution (do NOT flush the line); remove needle/cannula; elevate extremity. Apply dry warm compresses for 20 minutes 4 times daily for days 1-2. • **Preparation for Administration: Adult:** Solution for injection: The solution should be further diluted to concentrations as low as 0.5mg/ml in NS or D_5W; however, most clinicians generally dilute the dose in either 100 mL or 250 mL of NS or D_5W. **N.B.** Refer to manufacturer PIL for specific considerations.
Emetogenicity	**Adults:** - AUC ≥4: High (>90%). - AUC <4: Moderate (30% to 90%). **Pediatrics:** - ≥175 mg/m2/dose: High (>90%).

	Antiemetics may be recommended to prevent nausea and vomiting.
Warnings/ Precautions	• **Myelosuppression:** - It is the dose-limiting toxicity, usually manifested as thrombocytopenia and less commonly as leukopenia, neutropenia, and anemia. Risk factors include prior cytotoxic therapy (especially cisplatin), poor performance status, old age, impaired renal function, and concurrent myelosuppressive therapy. - Myelosuppression is dose and renal clearance dependent, so minimized by using the Calvert AUC-based dosing formula. - Blood transfusions due to anemia may be needed during prolonged carboplatin therapy. - If other concomitant myelosuppressive agents or radiation therapy are used, monitor carefully, dosing and time of administration should be managed to minimize additive toxic effects. - The median nadir typically occurs at day 21 for carboplatin as a single agent. **GI toxicity:** Nausea and vomiting may occur; antiemetics may be recommended to prevent nausea and vomiting. Nausea and vomiting may be more severe in patients who have received prior emetogenic chemotherapy. The incidence and severity of vomiting may be reduced by prophylactic antiemetics. **Hepatic function abnormalities:** High doses (>4 times the recommended dose) have resulted in severe abnormalities of LFTs. **Hypersensitivity/anaphylactoid reactions:** May occur within minutes of administration. Epinephrine, corticosteroids, and antihistamines have been used to treat symptoms. The risk of allergic reactions (including anaphylaxis) is increased in patients previously exposed to platinum therapy. Carboplatin therapy may be given with prophylactic corticosteroid and antihistamine, skin testing, and/or desensitization protocol. **Ototoxicity:** Ototoxicity may occur when administered concomitantly with aminoglycosides. Clinically significant hearing loss has been reported to occur in pediatric patients when therapy was administered at higher-than-recommended doses in combination with other ototoxic agents (eg, aminoglycosides). **Nephrotoxicity:** Mild and less common than with cisplatin; concomitant IV hydration may not be needed with carboplatin. The risk and severity of nephrotoxicity are increased with a high-dose carboplatin regimen, especially when given concurrently with other nephrotoxic chemotherapy. Dosage reduction or discontinuation of therapy is required in the presence of severe renal impairment.

	Disease-related concerns: Renal impairment: Patients with renal dysfunction are at increased risk for bone marrow suppression. **Neoplasms, benign, malignant, and unspecified** (including cysts and polyps): Secondary acute malignancies after cytostatic combination therapies containing Carboplatin have been reported. **Tumour lysis syndrome (TLS):** Patients at high risk of TLS, such as patients with high proliferative rate, high tumor burden, and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precautions taken. **Hemolytic uremic syndrome:** A life-threatening condition has been reported rarely that affects blood clotting functions and results in progressive kidney failure. Carboplatin should be discontinued at the first signs of rapidly falling hemoglobin with concomitant thrombocytopenia and elevation of kidney functions or LDH. Renal failure may not be reversible with discontinuation of therapy and dialysis may be required. **Neurotoxicity:** Peripheral neuropathy (e.g. Paresthesia) incidence or worsening is more common in patients over 65, receiving prolonged carboplatin therapy, or with prior cisplatin therapy. Neurologic evaluations should be performed regularly. Loss of vision (usually reversible within weeks of discontinuing) has been reported with higher-than-recommended doses. Loss of vision (usually reversible within weeks of discontinuing) has been reported with higher-than-recommended doses. **Concomitant use to take into consideration** - Ciclosporin (and by extrapolation Tacrolimus and Sirolimus): Excessive immunosuppression with risk of lymph proliferation. - Concurrent therapy with nephrotoxic or ototoxic drugs such as aminoglycosides, Amphotericin B, Vancomycin, Capreomycin, and diuretics, may increase or exacerbate toxicity, particularly in renal failure patients, due to carboplatin-induced changes in renal clearance. - Loop diuretics: Caution due to the cumulative nephrotoxicity and ototoxicity. - Combination therapy with other myelosuppressive agents may require dose changes or rescheduling of doses to minimize the additive myelosuppressive effects. - Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents may result in serious or fatal infections.
Storage and	• Store intact vials at 15°C to 30°C.

Light Sensitivity	• After dilution stability has been demonstrated for 24 hours at room temperature and 30 hours at 2-8°C if dilution has taken place in controlled and validated aseptic conditions. • Protect from light. **N.B.** Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• Tell your doctor if you have ever had an unusual or allergic reaction to cisplatin or mannitol before starting carboplatin treatment. • This drug induces low blood cell counts. Avoid infections and bleeding causes. • If you have an upset stomach, throwing up, diarrhea, or decreased appetite, talk with your doctor. There may be ways to lower these side effects. • Call your doctor if you experience signs of kidney problems like unable to pass urine, blood in the urine; hearing loss, or any other changes in hearing burning or numbness, or changes of eyesight. • This drug is teratogenic. Avoid getting pregnant during treatment with this medication. Fertility may be impaired.
Sequence of Administration	• Carboplatin is cell-cycle nonspecific. • Irritant. • When combined with Topotecan or Gemcitabine, Carboplatin should be given second to avoid toxicity. • When combined with Fluorouracil or Taxanes, Carboplatin may be given second for less toxicity.
Pharmaco-genomics	• **Excision Repair Cross-Complementing Rodent Repair Deficiency, Complementation Group 1 (Includes Overlapping Antisense Sequence)** - May alter the pharmacodynamics of Cisplatin and other platinum derivatives such as carboplatin, and oxaliplatin. - There is currently no clinically available test for ERCC1 polymorphisms as a predictor of clinical response to platinum compounds. Analysis is not currently recommended for routine use. • **Excision Repair Cross-Complementing Rodent Repair Deficiency, Complementation Group 2** - A rare inherited disorder, xeroderma pigmentosum, is associated with a high risk of malignancy particularly cancers associated with smoking (lung, bladder) or UV damage (melanoma). There is currently no clinically available test for ERCC2 polymorphisms; however, the clinical utility of cancer predisposition testing is unclear. Analysis is not currently recommended for routine use.

2. Cisplatin

Generic name	Cisplatin
Dosage Form/Strengths	Concentrate solution for infusion: 10mg/10ml, 10mg/20ml, 50mg/50ml, 50mg/100ml.
Route of Administration	Intravenous.
Pharmacologic Category	Antineoplastic Agent, Alkylating Agent; Platinum Analog ATC code: L01XA01.
Indications	**N.B.** *Refer to literature and specific protocols for all indications.* • Advanced or metastasized cases of: Testicular cancer, Ovarian cancer, Bladder carcinoma, Squamous cell carcinoma of the head and neck, non-small cell lung carcinoma, and small cell lung carcinoma. • Treatment of cervical carcinoma in combination with other chemotherapeutics or with radiotherapy. **Other indications:** Adrenocortical carcinoma, anal carcinoma, biliary tract cancer, breast cancer, endometrial carcinoma, esophageal cancer, gastric cancer, gestational trophoblastic neoplasia, Hodgkin lymphoma, pleural mesothelioma, multiple myeloma, neuroendocrine tumors, non-Hodgkin lymphoma, osteosarcoma, pancreatic cancer, penile cancer, primary CNS lymphoma, prostate cancer, thymic carcinoma, thymomas adenocarcinoma.
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols*. **Adult and pediatric dosing:** **For monotherapy,** the following two dosage regimens are recommended: • Single dose of 50 to 120 mg/m^2 every 3 to 4 weeks. • 15 to 20 mg/m^2 /day for five days, every 3 to 4 weeks **In combination therapy,** A typical dose is 20mg/m^2 or more once every 3 to 4 weeks. **In combination therapy for lung tumors**: 75-100 mg/m^2 every 3 to 4 weeks. **For treatment of cervical cancer,** Cisplatin is used in combination with radiotherapy. A typical dose is 40 mg/m^2 weekly for 6 weeks. **Hydration is necessary**: pre-hydration with 2 liters of an appropriate intravenous solution, and similar post-cisplatin hydration (recommended 2,500 mL/m^2 /24 hours) at a rate of 100 to 200 ml/ hour. If vigorous hydration is insufficient to maintain adequate urinary output, an osmotic diuretic may be administered (e.g. mannitol). Refer to the protocol used.
Dosage Adjustment	**N.B.** Refer to the protocol used for specific dose modifications. • **Dosing: Altered Kidney Function:**

	Due to nephrotoxicity concerns, alternative agents may be preferred in patients with baseline kidney impairment when clinically appropriate, or a dose reduction may be needed. The following recommendations have been found in the literature: ***Therapy with curative intent**:* - CrCl ≥60 mL/minute: IV: No dosage adjustment necessary. - CrCl 50 to <60 mL/minute: IV: Administer 75% of the usual recommended dose. - CrCl 40 to <50 mL/minute: IV**:** Administer 50% of the usual recommended dose. - CrCl <40 mL/minute: Use is not recommended. ***Therapy with palliative intent**:* - CrCl ≥60 mL/minute: IV: No dosage adjustment necessary. - CrCl 50 to <60 mL/minute: IV: Administer 75% of the usual recommended dose. - CrCl <50 mL/minute: Use is not recommended. • **Dosing: Hepatic Impairment:** No dosage adjustments are needed in patients with hepatic impairment.
Contra-indications	• Severe hypersensitivity to Cisplatin or other platinum-containing compounds. • Pre-existing renal impairment or hearing impairment. • Patients who are myelosuppressed or dehydrated.
Adverse Drug Reactions	• **Nephrotoxicity** • **Ototoxicity (up to 31%)** • **Neurotoxicity** • **High Emetogenic effects** • **Electrolyte disturbances** • **Myelosuppression** • **Sensitivity reactions** **>10%** **Central nervous system**: Neurotoxicity (peripheral neuropathy is dose and duration dependent) **Gastrointestinal**: Nausea and vomiting (76% to 100%) **Genitourinary**: Nephrotoxicity (28% to 36%; acute renal failure and chronic renal insufficiency) **Hematologic & oncologic**: Anemia (≤40%), leukopenia (25% to 30%; nadir: Day 18 to 23; recovery: By day 39; dose-related), thrombocytopenia (25% to 30%; nadir: Day 18 to 23; recovery: By day 39; dose-related). **Hepatic**: Increased liver enzymes. **Otic**: Ototoxicity (children 40% to 60%; adults 10% to 31%; as tinnitus, high-frequency hearing loss).

	1% to 10% **Local**: Local irritation.
Monitoring Parameters	**Prior and during treatment:** - CBC with differential. - Kidney function test (Monitor serum creatinine, BUN, CrCl) - Hepatic functions - Monitor serum electrolytes (calcium, magnesium, potassium, and sodium). - Monitor audiometry. • Monitor for signs of an infusion reaction. • Monitor closely for signs/symptoms of infection, hypersensitivity reactions, neuropathy, ocular toxicity, tumor lysis syndrome, and secondary malignancies.
Drug Interactions	***Risk X: Avoid combination*** Aminoglycosides, Abrocitinib, Baricitinib, BCG Products, Cladribine, Dengue Tetravalent Vaccine (Live), Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Mumps- Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Natalizumab, Netilmicin (Ophthalmic), Pimecrolimus, Poliovirus Vaccine (Live/Trivalent/Oral), Ritlecitinib, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Typhoid Vaccine, Upadacitinib Vaccines (Live), Yellow Fever Vaccine. **Risk D: Consider therapy modification** Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), Deferiprone, Denosumab, Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Taxane Derivatives, Topotecan, Vaccines (Inactivated/Non-Replicating). • **Interactions considerations:** - **Nephrotoxic substances:** will potentiate the toxic effect. - **Ototoxic substances:** will potentiate the toxic effect. - **Myelosuppressives or radiation:** will potentiate the toxic effect. - **Attenuated live vaccines:** not recommended. - **Oral anticoagulants:** regularly to check the INR. - **Antihistamines, Phenothiazines, and others:** may mask ototoxicity. - **Anticonvulsive substances:** serum concentrations may remain at subtherapeutic levels. - **Combination with bleomycin and vinblastine:** can lead to a Raynaud phenomenon.
Pregnancy and Lactation	**Pregnancy:** Avoid. There is positive evidence of human fetal risk. Gonadal suppression resulting in amenorrhoea or azoospermia may be irreversible and cause definitive infertility.

	Lactation: is not recommended as Cisplatin is excreted in human milk.
Administration	**Administration: IV:** - The Cisplatin solution should be administered by intravenous infusion throughout 6 to 8 hours. Do not administer as a rapid IV injection. - Administer appropriate pretreatment hydration and maintain adequate hydration and urinary output for 24 hours following cisplatin administration. - Needles or IV administration sets that contain aluminum should not be used in the preparation or administration; aluminum may react with cisplatin resulting in precipitate formation and loss of potency. • **Extravasation:** - Irritants may cause local skin reactions and chemical phlebitis. - Cisplatin is a vesicant at concentrations greater than 0.5 mg/mL; ensures proper needle or catheter placement before and during infusion; avoid extravasation. - Monitor infusion site during administration. • **Extravasation management:** If extravasation occurs, stop infusion immediately and disconnect (leave cannula/needle in place); gently aspirate extravasated solution (do NOT flush the line); remove needle/cannula; elevate extremity. Apply dry warm compresses for 20 minutes 4 times daily for 1-2 days. • **Preparation for administration**: Reconstituted solution should be further diluted in 1 to 2 L of a compatible infusion solution with or without 37.5 g of mannitol. N.B. Refer to manufacturer PIL for specific considerations.
Emetogenicity	• High (>90%) • Antiemetics are recommended to prevent nausea and vomiting.
Warnings/ Precautions	• **Nephrotoxicity:** - A major concern when prescribing Cisplatin is dose-related and cumulative and manifests as renal insufficiency, hypokalemia, and hypomagnesemia. and can cause severe renal toxicity, including acute renal failure. - A urine output of 100 mL/hour or greater will tend to minimize cisplatin nephrotoxicity. This can be accomplished by pre-hydration with 2 liters of an appropriate intravenous solution, and similar post cisplatin hydration (recommended 2,500 mL/m^2 /24 hours) at a rate of 100 to 200 ml/ hour. If vigorous hydration is insufficient to maintain adequate urinary output, an osmotic diuretic may be administered (e.g. mannitol). Refer to the protocol used. - Magnesium and Potassium supplementation may be needed. - **Amifostine** may be used to reduce the cumulative renal toxicity

associated with repeated administration of Cisplatin in patients with advanced ovarian cancer.

IV Amifostine 910 mg/m^2 once daily over 15 minutes 30 minutes before chemotherapy. Blood pressure should be monitored following administration. Interrupt administration if systolic blood pressure decreases significantly from baseline.

- **Neurotoxicity:**
  - Peripheral neuropathy is cumulative and usually reversible, although recovery is often slow. Caution at cumulative doses of more than 300mg/m^2. Manifestations include paresthesia, areflexia loss of proprioception, and vibratory sensation.
  - Neurologic symptoms have been reported after a single dose or maybe at delayed onset till 8 weeks after the last dose.
  - Perform a neurological examination before, during, and after completion of therapy.
  - When signs of neuropathy occur, consider discontinuation of Cisplatin.

- **Nausea and Vomiting:**

  Common and may be so severe that the drug must be discontinued. may be immediate and/or delayed, usually lasting up to 72 hours although may persist for up to 1 week.
- **Myelosuppression:**
  - Cisplatin may cause severe myelosuppression; fatalities due to infection (secondary to myelosuppression) have been reported.
  - Geriatric patients may be at higher risk for hematologic toxicity.
  - May require treatment interruption and/or dosage reduction.
- **Hypersensitivity Reactions:**
  - Cisplatin may cause severe hypersensitivity reactions, including anaphylaxis (some fatal). Manifestations include facial edema, wheezing, tachycardia, and hypotension.
  - Ensure supportive equipment and medications for the management of severe hypersensitivity reactions are available.
- **Ototoxicity:**
  - Ototoxicity is cumulative and irreversible and results from damage to the inner ear, including tinnitus, high-frequency hearing loss with or without clinical hearing loss, and occasional deafness. Vestibular toxicity has also been reported.
  - Ototoxicity can occur during or after treatment and can be unilateral or bilateral.
  - Consider audiometric and vestibular function monitoring.
- **Electrolyte disturbances:**
  - Can be serious and mainly includes hypomagnesemia, hypocalcemia, and hypokalemia.

	- Hypomagnesemia and or hypocalcemia may become symptomatic, with muscle irritability or cramps, clonus, tremor, carpopedal spasm, and/or tetany. Children may be at greater risk for developing hypomagnesemia. • **Ocular Toxicity:** - Optic neuritis, papilledema, and cortical blindness have been reported in patients receiving standard recommended doses of cisplatin for injection. - Improvement and/or total recovery usually occurs after discontinuing cisplatin for injection but can be delayed. • **Secondary Malignancies:** - The development of acute leukemia secondary to the use of cisplatin for injection has been reported. In these reports, cisplatin for injection was generally given in combination with other leukemogenic agents. • **Embryo-Fetal Toxicity:** - Based on human data, Cisplatin is teratogenic and embryotoxic in mice. - Advise females and males of reproductive potential to use effective contraception during treatment and for at least 6 months after the last dose of cisplatin for injection. • **Tumor lysis syndrome**: - Hyperuricemia has been reported with cisplatin; consider anti-hyperuricemic therapy to reduce uric acid levels.
Storage and Light Sensitivity	• Store intact vials at 20°C to 25°C. Do not refrigerate the solution (precipitate may form). • Protect from light. • The diluted solution is stable for 48 hours at 2 to 8°C when protected from light. **N.B** Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• The dose and timing of your chemotherapy may be changed based on the blood test results and/or other side effects. • Call your doctor if there are any symptoms of bleeding, infection, kidney disorders, neuropathy, or hearing disorders. • This drug is teratogenic, both male and female patients must use effective contraceptive methods during and for at least 6 months after the treatment with Cisplatin. May cause sterility in men and menopause in women. • You may bleed or get infected more easily. Be careful and avoid injury. • Talk with your doctor before getting any vaccines. Use of some vaccines with this drug may either raise the chance of an infection or make the vaccine not work as well.
Sequence of Administration	• A cell-cycle phase non-specific drug. • Irritants may cause local skin reactions and chemical phlebitis. • When combined with Irinotecan, Cisplatin should be given first for better response. • When combined with Taxanes, Topotecan, or Gemcitabine, Cisplatin should be given a second to avoid toxicity.

	• When combined with Fluorouracil, Cisplatin may be given second for maximum synergistic activity and less toxicity.
Pharmaco-genomics	TPMT – Cisplatin • Consider testing for TPMT gene variants when Cisplatin is prescribed to pediatric patients with cancer due to the association between TPMT loss-of-function alleles and an increased risk of Cisplatin-induced ototoxicity. Consider increased monitoring or alternative therapies in high-risk patients.

3. Oxaliplatin

Generic Name	Oxaliplatin
Dosage Form/Strengths	• Powder for Solution for I.V Infusion: 50mg, 100mg • Concentrate solution for infusion: 50 mg/10ml,100 mg/20ml, 200 mg /40 ml.
Route of Administration	IV
Pharmacologic Category	Antineoplastic Agent, Alkylating Agent; Platinum Analog. ATC Code: L01XA03
Indications	**N.B.** *Refer to literature and specific protocols for all indications.* • Adjuvant treatment of stage III colon cancer (in combination with infusion fluorouracil and leucovorin) after complete resection of primary tumor. • Treatment of advanced colorectal cancer (in combination with infusion fluorouracil and leucovorin). **Other indications:** Biliary tract cancer, chronic lymphocytic leukemia, esophageal cancer, gastric cancer, neuroendocrine tumors, non-Hodgkin lymphomas, ovarian cancer, pancreatic cancer, small bowel adenocarcinoma, and testicular cancer.
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols.* **Adult dosing** • **Colon cancer, stage III, adjuvant therapy** IV: 85 mg/m^2 on day 1 every 2 weeks (in combination with infusional fluorouracil/leucovorin) for up to 12 cycles. • **Colorectal cancer, advanced** IV: 85 mg/m^2 on day 1 every 2 weeks (in combination with infusional Fluorouracil/Leucovorin) until disease progression or unacceptable toxicity. The dosage given should be adjusted according to tolerability. **Pediatric dosing** The safety and effectiveness of pediatrics have not been established.
Dosage Adjustment	**N.B.** *Refer to the protocol used for specific dose modifications.* • **Altered Kidney Function: Adult** - Avoid severe impairment. - CrCl ≥30 mL/minute: No dosage adjustment necessary. - CrCl <30 mL/minute: Not recommended. • **Hepatic Impairment: Adult** There is no dosage adjustment provided. • **Toxicities Adjustments:** **Hematological**: Postpone treatment If hematological toxicity occurs (neutrophils < 1.5x10^9 /L or platelets < 50x10^9 /L), resume when acceptable

	blood counts. **Peripheral neuropathy**: - If troublesome symptoms last longer than seven days, **or** paraesthesia without functional impairment persists until the next cycle: Reduce subsequent Oxaliplatin from 85 to 65 mg/m^2 (metastatic setting) or 75 mg/m^2 (adjuvant setting). - If paraesthesia with functional impairment persists until the next cycle: Discontinue Oxaliplatin. Consider resumption after improvement.
Contra-indications	• Hypersensitivity to Oxaliplatin, other platinum-containing compounds, or any component of the formulation. • Myelosuppression before starting the first course, as evidenced by baseline neutrophils < 2 x 10^9/l and/or platelet count of < 100 x 10^9/l. • Peripheral sensory neuropathy with functional impairment before the first course. • Severely impaired renal function.
Adverse Drug Reactions	• **Peripheral Neuropathy** • **Myelosuppression** • **Hypersensitivity** **>10%:** **Gastrointestinal**: Abdominal pain (31%), anorexia (20%), constipation (31%), diarrhea (46%; grades 3/4: 4%), nausea (64%; grades 3/4: 4%), stomatitis (2% to 14%), vomiting (37%; grades 3/4: 4%). **Hematologic & oncologic**: Anemia (64%; grades 3/4: 1%), leukopenia (13%), thrombocytopenia (30%; grades 3/4: 3%). **Hepatic**: Increased serum alanine aminotransferase (36%), increased serum alkaline phosphatase (42%), increased serum aspartate aminotransferase (54%), increased serum bilirubin (13%). **Nervous system**: Fatigue (61%), headache (13%), insomnia (11%), pain (14%), peripheral neuropathy (76%, grades 3/4: 7%; acute: 65%, grades 3/4: 5%; delayed [persistent]: 43%, grades 3/4: 3%). **Neuromuscular & skeletal**: Back pain (11%). **Respiratory**: Cough (11%), dyspnea (13%). **Miscellaneous**: Fever (25%). **1% to 10%:** **Cardiovascular**: Chest pain (5%), edema (10%), flushing (3%), peripheral edema (5%), thromboembolism (2%). **Dermatologic**: Alopecia (3%), palmar-plantar erythrodysesthesia (1%), skin rash (5%). **Endocrine & metabolic**: Dehydration (5%), hypokalemia (3%). **Gastrointestinal**: Dysgeusia (5%), dyspepsia (7%), flatulence (3%), gastroesophageal reflux disease (1%), hiccups (2%). **Genitourinary**: Dysuria (1%). **Hematologic & oncologic**: Neutropenia (7%).

	Hypersensitivity: Hypersensitivity reaction (3%; including anaphylaxis, nonimmune anaphylaxis). **Local**: Injection-site reaction (9%, including erythema at injection site, pain at injection site, swelling at injection site). **Nervous system**: Dizziness (7%), rigors (9%). **Neuromuscular & skeletal**: Arthralgia (7%). **Ophthalmic**: Abnormal lacrimation (1%). **Renal**: Increased serum creatinine (5% to 10%). **Respiratory**: Epistaxis (2%), pharyngitis (2%), pharyngolaryngeal dysesthesia (grades 3/4: 1% to 2%), rhinitis (6%), upper respiratory tract infection (7%). **Frequency not defined:** **Gastrointestinal**: Dysphagia, gastrointestinal hemorrhage. **Genitourinary**: Hematuria. **Hematologic** & **oncologic**: Hemorrhage.
Monitoring Parameters	• CBC with differential and platelet count. • Liver function test (AST, ALT, Bilirubin). • ECG monitoring. • Electrolytes, including potassium and magnesium (before and periodically during treatment). • Monitor for signs/symptoms of hypersensitivity, pulmonary toxicity, posterior reversible encephalopathy syndrome (diagnosis is confirmed with MRI), bleeding, and GI toxicity. • Monitor for neuropathy and neurotoxicity symptoms.
Drug Interactions	***Risk X: Avoid combination:*** BCG (Intravesical) Cladribine, Dipyrone, Fexinidazole. ***Risk D: Consider therapy modification:*** Deferiprone, Lenograstim, Lipegfilgrastim, Palifermin, Ropeginterferon Alfa-2b, Taxane Derivatives, Topotecan.
Pregnancy and Lactation	**Pregnancy:** Contraindicated (First Trimester). Oxaliplatin may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies. Oxaliplatin may affect fertility in men and women. **Lactation:** Contraindicated due to the potential secretion into breast milk.
Administration	**Hazardous agent** (NIOSH 2016 [group 1]): Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. **Administration: IV:** - Administer as IV infusion over 2-6 hours. 6 hours is better to avoid acute toxicities. - Flush infusion line with glucose before administration of any concomitant medication.

	- Avoid exposure to cold temperatures, or consumption of cold food/beverages during or within hours after oxaliplatin infusion (may exacerbate acute neurological symptoms). - Do not use needles or administration sets containing aluminum. - When used in combination with a fluoropyrimidine (e.g., 5-FU), infuse oxaliplatin first. - Irritant with vesicant-like properties; ensure proper needle or catheter placement before and during infusion. Avoid extravasation; monitor the IV site for redness, swelling, or pain. **Extravasation:** Oxaliplatin is an irritant with vesicant-like properties; ensures proper needle or catheter placement before and during infusion; to avoid extravasation. **Extravasation management:** If extravasation occurs, stop infusion immediately and disconnect (leave cannula/needle in place); gently aspirate extravasated solution (do NOT flush the line); remove needle/cannula; elevate extremity. Apply dry warm compression for 20 minutes 4 times daily for days 1-2. **Preparation for Administration:** - Aqueous solution: Dilution with Dextrose D5W (250 or 500 mL) is required before administration. DO NOT dilute Oxaliplatin with saline or other solutions containing chloride ions. - Lyophilized powder: Use only SWFI or D5W to reconstitute powder. Obtain a concentration of 5 mg/mL. Gently swirl the vial to dissolve the powder. Dilution with D5W (250 or 500 mL) is required before administration. Discard the unused portion of the vial. **N.B**. Refer to manufacturer PIL for specific considerations
Emetogenicity	Pediatrics and Adults: Moderate (30% to 90%).
Warnings/ Precautions	**Bone marrow suppression:** Grade 3 and 4 neutropenia occurs commonly with oxaliplatin in combination with fluorouracil and leucovorin; sepsis, neutropenic sepsis, and septic shock have been reported with oxaliplatin (some fatal). Grade 3 and 4 thrombocytopenia has also occurred. **Cardiotoxicity:** QT prolongation and ventricular arrhythmias, including fatal torsades de pointes, have been reported with oxaliplatin. **Hemorrhage**: GI bleeding, hematuria, and epistaxis have been reported with oxaliplatin; there have been case reports of death due to intracerebral hemorrhage. Prolonged PT and INR occasionally associated with hemorrhage have been reported in patients also receiving anticoagulants while on oxaliplatin. Thrombocytopenia has been observed with oxaliplatin. **Hepatotoxicity:** Elevated transaminases and alkaline phosphatase have occurred with oxaliplatin. **Hypersensitivity:** Serious and fatal hypersensitivity reactions (including anaphylaxis) may occur within minutes of oxaliplatin administration and

	during any cycle. Grade 3 or 4 hypersensitivity has been observed (rare). Allergic reactions are like reactions reported with other platinum analogs and may occur with any cycle. **Neuropathy:** • Two types of peripheral sensory neuropathy may occur: The first type is an acute presentation (within hours to 2 days), reversible (resolves within 14 days), with primarily peripheral symptoms that are often exacerbated by cold temperatures or consuming cold food or beverages. • The second type of neuropathy is a more persistent (>14 days) presentation that usually is characterized by paresthesia, dysesthesias, and hypoesthesias and may interfere with daily activities (e.g., writing, swallowing, walking difficulties). These symptoms may improve in some patients upon discontinuing treatment. • Paresthesias that may interfere with functional activities can persist after up to 3 years following treatment cessation in the adjuvant setting. **Posterior reversible encephalopathy syndrome:** Cases have been reported rarely. Signs/symptoms include headache, mental status changes, seizure, blurred vision, blindness, and/or other vision changes; may be associated with hypertension. **Pulmonary toxicity:** Oxaliplatin is associated with pulmonary fibrosis (rare), which may be fatal. Pulmonary toxicity may present with dyspnea, cough, and/or hypoxia; grade 3 and 4 events have occurred. Eosinophilic pneumonia has been reported rarely. **Rhabdomyolysis:** Rhabdomyolysis (including fatal cases) has been reported with oxaliplatin. **Renal impairment** Patients with mild to moderate renal impairment should be closely monitored for adverse reactions and the dose adjusted according to toxicity
Storage and Light Sensitivity	• Store at room temperature, 15°C to 30°C. • Protect concentrated solution from light. • Solutions diluted for infusion do not require protection from light. • When diluted to 0.2mg/ml may be stored for 48 hours in 2-8 ^{0}C or for 6 hours at 20-25 ^{0}C. N.B. Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• Tell your doctor if you have any heart issues such as long QT on ECG, low magnesium levels, or low potassium levels, or if you take any medications as they may have this effect. • This medicine can cause neuropathy. Avoid exposure to cold temperatures, or consumption of cold food/beverages during or within hours after oxaliplatin infusion to avoid exacerbation of acute neurological symptoms. • Tell your doctor immediately about any respiratory symptoms, such as non-productive cough and dyspnea. Also, if any symptoms appeared of muscle toxicity, dark urine, decreased urine output, or the inability to urinate.

	• This drug may induce low blood cell counts. Avoid causes of infection and bleeding. • A very bad but reversible brain problem has happened with this drug. Call your doctor right away if you have signs like feeling confused, lowered alertness, a change in eyesight, seizures, or a very bad headache. • Avoid driving and doing other tasks or actions that call for you to be alert or have clear eyesight until you see how this drug affects you. • This drug is teratogenic, and carcinogenic and may affect fertility. • Oxaliplatin may cause delayed nausea and vomiting; antiemetics are recommended to prevent nausea and vomiting.
Sequence of Administration	• Cell cycle phase-specific. • Irritant with vesicant-like properties. • When combined with Taxanes or Gemcitabine, Oxaliplatin may be given second to decrease toxicity. • When combined with Fluorouracil, Oxaliplatin may be given first to give a synergistic effect.
Pharmaco-genomics	**Analysis is not currently recommended for routine use.** - Excision Repair Cross-Complementing Rodent Repair Deficiency, Complementation Group 1 (Includes Overlapping Antisense Sequence) - Excision Repair Cross-Complementing Rodent Repair Deficiency, Complementation Group 2 • **Glutathione-S-Transferase Pi:** Glutathione-S-transferase (GST) refers to a family of enzymes known to detoxify many electrophilic compounds, including carcinogens, chemotherapeutic drugs, and environmental toxins. Altered metabolism (ie, reduced detoxification) of drugs such as cyclophosphamide or platinum-containing compounds may result in increased cytotoxic activity and therefore increased therapeutic efficacy. • **X-Ray Repair Complementing Defective Repair in Chinese Hamster Cells 1:** May Alter Pharmacodynamics of Certain platinum-derivative chemotherapy (Carboplatin, Cisplatin, Oxaliplatin), 5-FU

E. Other Alkylating Agents

1. Dacarbazine

Generic name	Dacarbazine
Dosage Form/Strengths	Powder for solution: 100mg, 200mg
Route of Administration	IV
Pharmacologic Category	Antineoplastic Agent, Alkylating Agent ATC: L01AX04
Indications	**N.B.** *Refer to literature and specific protocols for all indications used.* **Hodgkin lymphoma:** Treatment of Hodgkin lymphoma (in combination with other chemotherapy agents). **Melanoma, metastatic malignant:** Treatment of metastatic malignant melanoma. ***Other indications:*** **Soft-tissue sarcomas**
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols.* **For the treatment of metastatic malignant melanoma** 250 mg/m^2 IV once daily for 5 days repeated every 3 weeks. **For the treatment of Hodgkin lymphoma** *Adults, Adolescents, and Children:* 375 mg/m^2 IV day on days 1 and 15 every 4 weeks in combination with other effective drugs.
Dosage Adjustment	**N.B.** *Refer to the protocol used for specific dose modifications.* **Dosing: Altered Hepatic Function: Adult** Dosage should be modified depending on clinical response and degree of hepatic dysfunction, but no quantitative recommendations are available. Severe impairment: Use is not recommended. **Dosing: Altered Kidney Function: Adult** CrCl ≥30 mL/minute: No dosage adjustment is necessary. CrCl <30 mL/minute: Consider reducing the dose to 70% of the usual dose. Hemodialysis: Consider reducing the dose to 70% of the usual dose.
Contra-indications	Dacarbazine (DTIC) hypersensitivity
Adverse Drug Reactions	**Bone marrow suppression:** Hemopoietic depression is the most common toxicity with Dacarbazine. **Hepatic effects:** Hepatic necrosis has been reported. **Carcinogenic/teratogenic:** This agent has a carcinogenic and teratogenic effect. **Frequency is not always defined.** **Central nervous system**: Infusion-site pain

	Dermatologic: Alopecia **Gastrointestinal**: Nausea and vomiting (>90%), anorexia **Hematologic and oncologic**: Bone marrow depression (onset: 5 to 7 days; nadir: 7 to 10 days; recovery: 21 to 28 days), leukopenia, thrombocytopenia
Monitoring Parameters	• CBC. • Liver function tests. • Renal function test. • Monitor infusion site.
Drug Interactions	***Risk X: Avoid combination*** Abrocitinib Baricitinib BCG (Intravesical) Cladribine Dengue Tetravalent Vaccine (Live) Deucravacitinib Dipyrone Fexinidazole Filgotinib Natalizumab Pimecrolimus Poliovirus Vaccine (Live/Trivalent/Oral) Rubella- or Varicella-Containing Live Vaccines Ruxolitinib (Topical) Tacrolimus (Topical) Talimogene Laherparepvec Tertomotide Tofacitinib Typhoid Vaccine Upadacitinib Vaccines (Live) Yellow Fever Vaccine ***Risk D: Consider therapy modification*** Test COVID-19 Vaccine (Adenovirus Vector) COVID-19 Vaccine (mRNA) Deferiprone Denosumab Fotemustine Influenza Virus Vaccines Leflunomide Lenograstim Lipegfilgrastim Palifermin Polymethylmethacrylate Rabies Vaccine Ropeginterferon Alfa-2b Sipuleucel-T Vaccines (Inactivated/Non-Replicating)
Pregnancy and Lactation	**Pregnancy**: In general, if chemotherapy is indicated, it should be avoided during in the first trimester; there should be a 3-week time period between the last chemotherapy dose and anticipated delivery, and chemotherapy should not be administered beyond week 33 of gestation. For patients with advanced-stage disease, ABVD can be administered in the second and third trimesters. **Lactation**: Due to the potential for serious adverse reactions in the breastfed infant, a decision should be made to discontinue Dacarbazine or to discontinue breastfeeding, considering the benefits of treatment to the mother.
Administration	**Hazardous** agent: NIOSH 2016 List, Group 1: Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. **Rate of infusion:** • Infuse over 15 to 60 minutes; rapid infusion may cause severe venous irritation. Other infusion durations have been reported; refer to literature and/or regimen for infusion details (may vary by protocol). • Dacarbazine is an irritant; local reactions may occur. Monitor infusion site. **Preparation of IV administration:** • Reconstitute 100 mg and 200 mg vials with 9.9 mL and 19.7 mL SWFI, respectively, resulting in a concentration of 10 mg/mL; some institutions use different standard dilutions (eg. 20 mg/mL). May further dilute in D5W or NS. Exposure to light results in loss of activity; the amount of degradation varies based upon condition; protect from light. N.B. Refer to manufacturer PIL for specific considerations.

Emetogenicity	High emetic Risk: Administer routine antiemetic prophylaxis before treatment.
Warnings/ Precautions	• **Anaphylaxis**: This may occur following dacarbazine administration. • **Bone marrow suppression**: Hematologic toxicity is the most common dacarbazine toxicity. Leukopenia and thrombocytopenia may be severe; anemia may also occur. The onset for leukopenia is about 14 days (range: 10 to 30 days) and the duration is 1 to 3 weeks. The onset for thrombocytopenia is about 18 days (range: 12 to 30 days) and the duration is 1 to 3 weeks. • **Extravasation**: Dacarbazine is an irritant; local reactions may occur. extravasation may result in tissue damage and severe pain. • **Hepatotoxicity**: Hepatotoxicity usually occurs with combination chemotherapy but may occur with Dacarbazine alone.
Storage and Light Sensitivity	• The reconstituted solution (in the vial) should be used within 72 hours if refrigerated and 8 hours if at room temperature. • Following dilution for infusion (in D5W or NS), solutions may be stored for up to 24 hours refrigerated (4°C) or for up to 8 hours at normal room conditions when protected from light. • Dacarbazine is light-sensitive. Protect from light. Exposure to light results in loss of activity **N.B**. Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• This drug induces low blood cell counts. Avoid infections and bleeding causes. • Liver problems have rarely happened with this drug. Call a doctor if signs of liver problems appear e.g. dark urine, tiredness, decreased appetite, upset stomach or stomach pain, light-colored stools, throwing up, or yellow skin or eyes. • This drug is Carcinogenic. Teratogenic. Emetogenic.
Sequence of Administration	• Cell cycle non-specific. • Irritant. • When combined with gemcitabine, dacarbazine may be administered first for less toxicity.

ANTIMETABOLITES

A. Antifolate

1. Methotrexate

Generic name	Methotrexate
Dosage Forms/ Strengths	• Tablets: 2.5mg, 5mg, 7.5mg, 10mg, 15mg. • Solution for injection (IV, IM, SC, Intrathecal): 50mg/2ml, 5000 mg/50ml. • Lyophilized Powder: 50mg • Solution for injection in Pre-filled Syringe: 7.5 mg/0.15 ml, 10 mg/0.2 ml, 15 mg/0.3 ml, 20 mg/0.4 ml, 25 mg/ 0.5 ml.
Route of Administration	Oral, Intravenous, Intramuscular, Intrathecal, Subcutaneous.
Pharmacologic Category	Antineoplastic Agent, Antimetabolite (Antifolate); Antirheumatic, Disease Modifying; Immunosuppressant Agent. ATC code: **Antineoplastic**: L01BA01, **Immunosuppressants**: L04AX03.
Indications	**N.B.** *Refer to literature and specific protocols for all indications*. **Non-oncology uses.** • Active rheumatoid arthritis in adult patients. • Polyarthritic forms of severe, active juvenile idiopathic arthritis, when the response to nonsteroidal anti-inflammatory drugs (NSAIDs) has been inadequate, • Psoriasis: Severe recalcitrant disabling psoriasis which is not adequately responsive to other forms of therapy, and severe psoriatic arthritis in adult patients. • Mild to moderate Crohn's disease in adult patients refractory or intolerant to thiopurines. **Oncology Uses** • Acute lymphocytic leukemia (acute lymphoblastic leukemia). • Prophylaxis of meningeal leukemia. • Non-Hodgkin's lymphomas. • Osteogenic sarcoma. • Breast cancer: Adjuvant and in advanced disease. • Head and neck cancer: Metastatic or recurrent. • Choriocarcinoma and similar trophoblastic diseases. • Urinary bladder: Advanced disease. • Cervical, ovarian, and testicular carcinoma • Mycosis fungoides treatment.
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols.* **N.B.** Administer folic acid to reduce the risk of methotrexate adverse reactions.

- **Rheumatoid Arthritis:**
  - **Initial, Oral/S.C**: 7.5 mg as a single weekly dose. The initial dose may be increased gradually by 2.5 mg per week. Do not exceed 20-25 mg weekly.
  - Upon achieving the therapeutically desired result, reduce the dose gradually to the lowest possible effective maintenance dose.
- **Polyarthritic forms of juvenile idiopathic arthritis:**
  - **S.C/Oral**: 10-15 mg/m² body surface area (BSA)/once weekly. In therapy-refractory cases, the dose may be increased up to 20mg/m².
  - Upon achieving the therapeutically desired result, reduce the dose gradually to the lowest possible effective maintenance dose.
  - Use in children < 3 years of age is not recommended as insufficient data on efficacy and safety.
- **Psoriasis:**
  - **Before therapy**: 5 – 10 mg parenterally, one week before therapy to detect idiosyncratic adverse reactions.
  - **Initial S.C/Oral/IM/IV**: 7.5-15 mg weekly; adjusted according to response and toxicity not to exceed 25 mg weekly.
  - Upon achieving the therapeutically desired result, reduce the dose gradually to the lowest possible effective maintenance dose.
- **Crohn's Disease:**
  - **Induction treatment S.C**: 25 mg/week.
  - **Maintenance treatment S.C**: 15 mg/week.
    Use in children is not recommended for Crohn's disease.
- **Mycosis fungoides (cutaneous T-cell lymphoma):**
  - **Oral:** 2.5-10 mg daily
  - **IM**: 50 mg weekly or 25mg twice weekly.
    Adjust dose according to response and hematological toxicity.
- **Non-Hodgkin Lymphoma:**
  In combination therapy: **IV**: Dosages range from 10 mg/m² to 8000 mg/m².
  As a single agent:
  - **For central nervous system-directed therapy**: IV: 8,000 mg/m² over 4 hours infusion.
  - **For cutaneous forms of non-Hodgkin lymphoma**: IV: 5 to 75 mg
- **Acute Lymphoblastic Leukemia:**
  - **IV:** The dosage varies from 10 to 5000 mg/m². use Leucovorin rescue in high doses.
  - The maintenance dose for ALL is 15-30 mg/m² once or twice weekly orally or IM.
  - **Other examples of dosing**: Oral: 3.3 mg/m² in combination with another cytostatic agent once daily for 4-6 weeks. IV: 2.5 mg/kg every

week. High dose regimen between 1 to 12 g/m^2 (IV. 1-6 h) repeated every 1-3 weeks.
  - **Intrathecal:** 12 to 15 mg (maximum 15 mg/dose) every 2 to 7 days; continue for 1 dose beyond cerebrospinal fluid (CSF) cell count normalization.
    Age: <1 year: Dose 6 mg, Age: 1 year: Dose 8 mg, Age: 2 years: Dose 10 mg, Age: 3 or older year: Dose 12 mg.
- **Breast cancer:**
  - **IV:** 40 mg/m^2 days 1 and 8 every 3 weeks (in combination with cyclophosphamide and fluorouracil).
  - **IV**: 10-60 mg/m^2 can be used with other combination regimens for advanced disease.
- **Osteosarcoma:**
  - **IV**: 8-12 g/m^2 (may increase to 15 gm/m^2 (maximum 20 g/dose) to produce a peak serum methotrexate concentration of 1,000 micromolar (10^{-3} mol/L) at the end of the methotrexate infusion,) over 4 hours as single or combination regimens.
  - Administer leucovorin rescue by high-dose methotrexate regimen guidelines.
- **Head and neck cancer (squamous cell carcinoma):**
  - **IV bolus**: 40-60 mg/m^2 once weekly until disease progression or unacceptable toxicity.
- **Advanced squamous epithelial and bladder cancer:**
  - **IV**: 100-200 mg/m^2
- **Gestational Trophoblastic Neoplasia GTN:**
  - **For patients with low-risk GTN:** IM or IV: 30 mg/m^2 to 200 mg/m^2 or 0.4 mg/kg to 1 mg/kg.
  - **For patients with high-risk GTN:** IV infusion: 300 mg/m^2 over 12 hours as a component of a multi-drug regimen**.**
- **Burkitt's tumor Lymphoma:**
  - **Stage 1-2**: **Oral**: 10-25 mg per day orally for 4 to 8 days.
  - **Stage 3**: 0.625 mg to 2.5 mg/kg daily in combined drug therapy.

Dosage Adjustment

N.B. *Refer to the protocol used for specific dose modifications.*

- **Dosing: Altered Kidney Function: Adult and pediatric:**

For methotrexate doses <100mg/m^2

- CrCl >60 mL/minute: No dose adjustment necessary.
- CrCl 30 to 59 mL/minute: Administer 50% of the dose.
- CrCl <30 mL/minute: Avoid use.

For methotrexate doses >100mg/m^2

- CrCl >80 mL/minute: No dose adjustment necessary.
- CrCl 60 to 80 mL/minute: Administer 60-75% of dose.
- CrCl <60 mL/minute: Avoid use.

	• **Dosing: Hepatic Impairment: Adult and pediatric** – Use with caution and consider a reduced dose in patients with impaired hepatic function or preexisting hepatic damage. **The following adjustments have been recommended:** • Bilirubin 3.1 to 5 mg/dL **or** transaminases >3 times ULN: Administer 75% of dose. • Bilirubin >5 mg/dL: Avoid use. • Hepatotoxicity during treatment: Withhold, consider a reduced dose, or discontinue methotrexate as appropriate.
Contra-indications	• History of severe hypersensitivity to methotrexate or any component of the formulation • Pregnancy or breastfeeding (in non-oncological indications). • Alcohol use disorder • Severe liver or renal disease, • Immunodeficiency syndromes (overt or laboratory evidence) • Serious, acute, or chronic infections such as tuberculosis and HIV. • Preexisting blood dyscrasias (e.g., bone marrow hypoplasia, leukopenia, thrombocytopenia, significant anemia).
Adverse Drug Reactions	• **Alimentary System:** gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal ulceration and bleeding, enteritis, pancreatitis. • **Blood and Lymphatic System Disorders:** suppressed hematopoiesis, anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia, thrombocytopenia, agranulocytosis, eosinophilia, lymphadenopathy, and lymphoproliferative disorders (including reversible). • **Hepatobiliary Disorders:** hepatotoxicity, acute hepatitis, chronic fibrosis, and cirrhosis, hepatic failure, decrease in serum albumin, liver enzyme elevations. • **Infection:** There have been case reports of sometimes fatal opportunistic infections in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases. Pneumocystis jiroveci pneumonia was the most common opportunistic infection. There have also been reports of infections, pneumonia, cytomegalovirus infection, including cytomegaloviral pneumonia, sepsis, fatal sepsis, nocardiosis; histoplasmosis, cryptococcosis, Herpes zoster, Herpes simplex hepatitis, and disseminated Herpes simplex. • **Pulmonary System:** respiratory fibrosis, respiratory failure, alveolitis, and interstitial pneumonitis deaths have been reported, and chronic interstitial obstructive pulmonary disease has occasionally occurred. • **Urogenital System:** severe nephropathy or renal failure, azotemia, cystitis, hematuria, proteinuria; defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge, and

gynecomastia; infertility, abortion, fetal death, fetal defects.

- **Central Nervous System:** headaches, drowsiness, blurred vision, transient blindness, speech impairment including dysarthria and aphasia, hemiparesis, paresis, and convulsions have also occurred following administration of methotrexate or unusual cranial sensations, leukoencephalopathy, or encephalopathy.
- **Skin:** erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, skin necrosis, skin ulceration, and exfoliative dermatitis.
- **Cardiovascular:** pericarditis, pericardial effusion, hypotension, and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus).

>10%:

Gastrointestinal: Diarrhea (16%), nausea (31%), oral mucosal ulcer (11%), vomiting (≤11%)
Hepatic: Hepatic cirrhosis (chronic therapy; <1% to ≥10%), hepatotoxicity (≥10%), increased liver enzymes (14% to 15%;)
Nervous system: Dizziness (13%), fatigue (31%), headache (19%)
Respiratory: Cough (16%)

1% to 10%:

Dermatologic: Alopecia (≤10%), burning sensation of skin (psoriasis: 3% to 10%), dermatitis (rheumatoid arthritis: 1% to 3%), pruritus (9%), skin photosensitivity (3% to 10%), skin rash (≤3%)
Endocrine & metabolic: Weight loss (5%)
Gastrointestinal: Anorexia (4%), sore throat (8%), stomach pain (9%), stomatitis (2% to 10%)
Hematologic & oncologic: Anemia (3%), leukopenia (1% to 3%; WBC <3000/mm^3), neutropenia (≤1%), pancytopenia (rheumatoid arthritis: 1% to 3%), thrombocytopenia (rheumatoid arthritis: 3% to 10%; platelet count <100,000/mm^3)
Hepatic: Hepatic fibrosis (chronic therapy: ≥4% to <10%)
Infection: Chest infection (3%)
Ophthalmic: Blurred vision (5%)
Respiratory: Dyspnea (6%), interstitial pneumonitis (rheumatoid arthritis: 1%)
Miscellaneous: Fever (3%)

Monitoring Parameters	**In all cases: (oncological and non-oncological):** • CBC with differential and platelets.

	• Liver and renal function tests. • Chest x-ray (within 1 year before initiation) • Hepatitis B and C serology if clinically indicated. • Serum methotrexate level monitoring can (depending on dosage or therapy protocol). • Monitor for toxicity during treatment including pulmonary toxicity as the patients may have a dry cough, fever, and dyspnea, and monitor mouth and throat for mucosal changes.
Drug Interactions	• ***Risk X: Avoid combination:*** Abrocitinib, Acitretin, Aminolevulinic Acid (Systemic), BCG (Intravesical), Brivudine, Cladribine, Dengue Tetravalent Vaccine (Live), Deucravacitinib, Dichlorphenamide, Dipyrone, Fexinidazole, Filgotinib, Foscarnet, Mumps-Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Natalizumab, Nitrous Oxide, Pimecrolimus Poliovirus Vaccine (Live/Trivalent/Oral), Ritlecitinib, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Taurursodiol, Tertomotide, Yellow Fever Vaccine. • ***Risk D: Consider therapy modification:*** Alcohol (Ethyl), Baricitinib, Coccidioides immitis Skin Test, COVID-19 Vaccines, Dapsone (Systemic), Deferiprone, Denosumab, Dexketoprofen, Influenza Virus Vaccines, Inhibitors of the Proton Pump (PPIs and PCABs), Leflunomide, Lenograstim, Lipegfilgrastim, Nonsteroidal Anti-Inflammatory Agents, Palifermin, Pemetrexed, Polymethylmethacrylate, Probenecid, Rabies Vaccine, Ropeginterferon Alfa-2b, Salicylates, Sipuleucel-T, Sulfonamide Antibiotics, Tofacitinib, Trimethoprim, Upadacitinib, Vaccines (Inactivated/Non-Replicating), Vaccines (Live). **Notes:** **NSAIDs**: In concomitant treatment with Methotrexate (usually at a high dose), Unexpected severe (including fatal) myelosuppression, aplastic anemia, and gastrointestinal toxicity have been reported. **Proton pump inhibitors:** Co-administration of proton pump inhibitors and Methotrexate (especially at high doses), may result in toxicity due to elevated and prolonged plasma levels of methotrexate and/or its metabolite. **Trimethoprim/Sulfamethoxazole:** may increase myelosuppression of Methotrexate, probably due to reduced tubular secretion and/or an additive antifolate effect.
Pregnancy and Lactation	**Pregnancy:** Methotrexate is contraindicated in pregnancy in non-oncological diseases. It can cause embryo-fetal toxicity, including fetal death. When used in oncological indications, methotrexate should not be administered during pregnancy during the first trimester of pregnancy. Methotrexate may decrease fertility, mostly reversible after discontinuation.

	Lactation: Breastfeeding should be discontinued during treatment and for 1 week after the final methotrexate dose.
Administration	**Hazardous agent** (NIOSH 2016 [group 1]): Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. • **Administration: IM** May be administered at a concentration ≤25 mg/mL; autoinjectors should not be used for IM administration. • **Administration: Oral** Administer on an empty stomach (at least 1 hour before or 2 hours after food or drink except water). • **Administration: Subcutaneous** May be administered SUBQ (depending on indication and product). Autoinjectors or prefilled syringes for once-weekly SUBQ use in the abdomen or thigh; the patient may self-administer after appropriate training and with appropriate follow-up monitoring. • **Administration: IV** **Slow push** at a concentration ≤25 mg/mL and rate ≤ 10 mg/minute. **Bolus infusion,** or **24-hour continuous infusion** (route and rate of administration depends on indication and/or protocol). Must use preservative-free formulation for high-dose methotrexate. **Preparation for IV administration:** **Powder for injection**: Reconstitute with sterile preservative-free D5W or NS to a concentration of 50 mg/mL; further dilute in D5W or NS. **Solution for injection** (25 mg/mL): May further dilute in D5W or NS. • **Administration: Intrathecal** May be administered intrathecally; must use a preservative-free formulation for intrathecal administration. **N.B**. Refer to manufacturer PIL for specific considerations.
Emetogenicity	**IV:** • ≥250 mg/m^2: Moderate (30% to 90%). • >50 to <250 mg/m^2: Low (10% to 30%). • ≤50 mg/m^2: Minimal (<10%). **Oral:** Minimal or low (<30%).
Warnings/ Precautions	**Gastrointestinal** • If vomiting, diarrhea, or stomatitis occur, which may result in dehydration, Methotrexate should be discontinued until recovery occurs.

- Hemorrhagic enteritis and fatal intestinal perforation have been reported.
- Methotrexate should be used with extreme caution in the presence of peptic ulcer disease or ulcerative colitis.

Myelosuppression

- Methotrexate suppresses hematopoiesis and can cause severe and life-threatening pancytopenia, anemia, leukopenia, neutropenia, and thrombocytopenia.
- Obtain blood counts at baseline, periodically during treatment, and as clinically indicated.
- Patients with profound granulocytopenia and fever should be evaluated immediately and usually require parental broad-spectrum antibiotic therapy.
- Methotrexate should be stopped immediately if there is a significant drop in blood counts.

Hepatic Toxicity

- Methotrexate can cause severe and potentially irreversible hepatotoxicity, including fibrosis, cirrhosis, and fatal liver failure.
- Special caution is indicated in the presence of preexisting liver damage or impaired hepatic function.
- Monitor liver tests at baseline, periodically during treatment, and as clinically indicated.

Infections

- Patients treated with methotrexate are at increased risk for developing life-threatening or fatal bacterial, fungal, or viral infections, including opportunistic infections.
- Monitor patients for infection during and after treatment with Methotrexate.
- Withhold or discontinue Methotrexate for serious infections considering the importance of Methotrexate treatment.

Neurotoxicity

- Methotrexate can cause severe acute and chronic neurotoxicity, which can be progressive, irreversible, and fatal.
- There have been reports of leukoencephalopathy following intravenous administration of methotrexate to patients who have had craniospinal irradiation.
- Manifestations of this stroke-like encephalopathy may include confusion, hemiparesis, transient blindness, seizures, and coma.
- Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (1 gm/m2).
- The intrathecal use of methotrexate can cause central nervous system

toxicity which may be classified as follows: acute chemical arachnoiditis manifested by headache, back pain, nuchal rigidity, and fever; sub-acute myelopathy characterized by paraparesis/paraplegia associated with involvement with one or more spinal nerve roots.

- Monitor patients for neurotoxicity and withhold or discontinue Methotrexate.

Pulmonary toxicity

- Methotrexate-induced lung disease, including acute or chronic interstitial pneumonitis, is a potentially dangerous lesion, which may occur acutely at any time during therapy and has been reported at low doses.
- The typical methotrexate-induced lung disease symptoms include fever, cough, dyspnea, hypoxemia, and an infiltrate on chest X-ray; infection (including pneumonia).
- Monitor patients for pulmonary toxicity and withhold or discontinue Methotrexate.

Renal toxicity

- High doses of methotrexate used in the treatment of osteosarcoma may cause renal damage leading to acute renal failure.
- Close attention to renal function including adequate hydration, urine alkalinization, and measurement of serum methotrexate and creatinine levels are essential for safe administration.

Skin

- Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme, have been reported in children and adults, within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration.
- Exposure to ultraviolet radiation while taking methotrexate may aggravate psoriasis.
- Methotrexate can cause radiation recall dermatitis and photodermatitis (sunburn) reactivation.

Methotrexate and pleural effusion/ascites

- Methotrexate is eliminated slowly from collections of fluid (e.g. pleural effusion, ascites). This results in a prolonged terminal half-life and unexpected toxicity.
- In patients with significant accumulations of fluid, it is advisable to evacuate the fluid before treatment and to monitor plasma methotrexate levels.

Calcium folinate rescue

- o Refer to the applied protocol of intermediate or high-dose methotrexate administration

Folic Acid Supplementation

	• Products containing folic acid, or its derivatives may decrease the clinical effectiveness of methotrexate. While Folate deficiency may increase methotrexate adverse reactions. Administer folic acid or folinic acid for patients with rheumatoid arthritis, PJIA, and psoriasis. **Hypersensitivity Reactions** • Hypersensitivity reactions, including anaphylaxis, can occur with methotrexate. • If anaphylaxis or other serious hypersensitivity reaction occurs, immediately and permanently discontinue Methotrexate. **Immunization and Risks Associated with Live Vaccines** • Disseminated infections following administration of live vaccines have been reported. • The interval between live vaccinations and initiation of methotrexate should be by current vaccination guidelines regarding immunosuppressive agents. • Immunization with live vaccines is not recommended during treatment. **Lymphoma** • Malignant lymphoma, which can go into remission after discontinuation of the treatment with methotrexate can occur in patients on low-dose therapy and may not therefore require any cytotoxic treatment. • Methotrexate should be discontinued first, and appropriate treatment initiated if the lymphoma does not regress. **Radiotherapy** • Concomitant methotrexate treatment and radiotherapy can increase the risk of soft tissue necrosis and osteonecrosis.
Storage and Light Sensitivity	• **IV, IM, or SC:** Store intact vials, autoinjectors, and prefilled syringes between 15°C and 30°C. The diluted product is chemically and physically stable in both diluents at both concentrations for 36 hours at 20-25°C and 35 days at 2-8°C. Solution diluted for infusion in D5W, or NS may be stored for 4 to 24 hours at room temperature or up to 24 hours refrigerated at 2°C to 8°C. • **Oral:** Tablets: Store between 15°C and 30°C. • Protect from light. N.B. Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• This medicine may affect blood cell count. Avoid causes of infection and bleeding. Some medications such as NSAIDs may increase your risk of bleeding. • Methotrexate treatment may get you sunburned more easily. Avoid sun, sunlamps, and tanning beds. Use sunscreen and wear clothing and eyewear that protects you from the sun. • Tell your doctor If you are taking a product that has folic acid or folinic acid

	in it. • Avoid driving and doing other tasks or actions that call for you to be alert until you see how this drug affects you. • Talk with your doctor before getting any vaccines. Use of some vaccines with this drug may either raise the chance of an infection or make the vaccine not work as well. • Avoid pregnancy and breastfeeding during treatment with this medicine.
Pharmaco-genomics	• **Methylenetetrahydrofolate Reductase:** Methylenetetrahydrofolate reductase regulates the intracellular folate pool which is used in the synthesis of DNA and protein.
Sequence of Administration	• Cell cycle specific for the S phase of the cycle. • Nonvesicant

2. Pemetrexed

Generic name	Pemetrexed
Dosage Forms/Strengths	Concentrate for solution for I.V. Infusion: 500 mg/20 ml, 1000 mg/40 ml. Powder for concentrate for solution for I.V Infusion: 100mg, 500 mg.
Route of Administration	IV
Pharmacologic Category	Antineoplastic Agent, Antimetabolite (Antifolate) ATC: L01BA04
Indications	**N.B.** Refer to literature and specific protocols for all indications **Malignant pleural mesothelioma:** Treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma (in combination with Cisplatin). **Non-small cell lung cancer (**NSCLC) • Used for locally advanced or metastatic non-squamous non-small cell lung cancer (as first line in combination with Cisplatin **or** second line as monotherapy). • In combination with Pembrolizumab and Platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous non-small cell lung cancer, with no EGFR or ALK genomic tumor aberrations. • As monotherapy for maintenance treatment of locally advanced or metastatic non-squamous non-small cell lung cancer in patients whose disease has not progressed following platinum-based chemotherapy.
Dosage Regimen	**N.B.** Different doses and regimens have been used; consult the literature for specific protocols **Adult dosing (monotherapy or in combinations)** **IV infusion**: 500 mg/m^2 over 10 minutes on the first day of each 21-day cycle until disease progression or unacceptable toxicity. Cisplatin 75 mg/m^2 BSA is infused over two hours approximately 30 minutes after completion of the Pemetrexed infusion. **To reduce treatment-related toxicity** • Initiate folic acid 400 mcg to 1000 mcg orally, once daily, 1 week before the first dose of Pemetrexed Injection, and continue until 21 days after the last dose of Pemetrexed Injection. • Administer vitamin B12, 1 mg IM, 1 week before the first dose of Pemetrexed Injection and every 3 cycles. • Administer dexamethasone 4 mg orally, twice daily the day before, the day of, and the day after Pemetrexed Injection administration. **Pediatrics** Pemetrexed Injection is not safe and effective in children.
Dosage Adjustment	**N.B.** Refer to the protocol used for specific dose modifications. **Dosing: Altered Kidney Function: Adult**

	• CrCl ≥45 mL/minute: No dosage adjustment necessary. • CrCl <45 mL/minute: Use is not recommended. **Dosing: Hepatic Impairment: Adult** • There are no dosage adjustments recommended. • Patients with a hepatic impairment such as bilirubin > 1.5 times the upper limit of normal and/or aminotransferase > 3.0 times the upper limit of normal or > 5.0 times the upper limit of normal for liver metastatic patients have not been studied. **Hematologic toxicities:** • ANC <500/mm3 and platelets ≥50,000/mm3: Reduce pemetrexed dose to 75% of previous dose. • Platelets <50,000/mm3 without bleeding: Reduce the pemetrexed dose to 75% of the previous dose. • Platelets <50,000/mm3 with bleeding: Reduce the pemetrexed dose to 50% of the previous dose. **Non-hematologic toxicities:** • Grade 3 or 4 neurotoxicity: Permanently discontinue Pemetrexed. • Grade 3 or 4 toxicities (excluding neurotoxicity): Withhold until resolution. Then resume as follows: • Grade 3 or 4 toxicity (excluding mucositis and neurotoxicity): Reduce the pemetrexed dose to 75% of the previous dose. • Grade 3 or 4 diarrhea or any diarrhea requiring hospitalization: Reduce the pemetrexed dose to 75% of the previous dose. • Grade 3 or 4 mucositis: Reduce the pemetrexed dose to 50% of previous dose.
Contra-indications	Severe hypersensitivity to pemetrexed or any component of the formulation.
Adverse Drug Reactions	**>10%** **Dermatologic**: Desquamation (≤14%), skin rash (≤14%). **Gastrointestinal**: Anorexia (19% to 22%), diarrhea (5% to 13%; grades 3/4: 1%), nausea (12% to 31%; grades 3/4: ≤3%), stomatitis (≤15%; grades 3/4: ≤1%), vomiting (6% to 16%; grades 3/4: 2%). **Hematologic & oncologic**: Anemia (15% to 19%; grades 3/4: 3% to 5%), neutropenia (6% to 11%; grades 3/4: 3% to 5%). **Nervous system**: Fatigue (18% to 34%). **Respiratory**: Pharyngitis (≤15%). **1% to 10%** **Cardiovascular**: Edema (5%). **Dermatologic**: Alopecia (6%), erythema multiforme (<5%), pruritus (7%). **Gastrointestinal**: Abdominal pain (1% to 5%), constipation (6%). **Hematologic & oncologic**: Febrile neutropenia (<5%), thrombocytopenia (8%; grades 3/4: 2%). **Hepatic**: Increased serum alanine aminotransferase (8% to 10%), increased

	serum aspartate aminotransferase (7% to 8%). **Hypersensitivity**: Hypersensitivity reaction (<5%). **Infection**: Infection (5%). **Nervous system**: Neuropathy (sensory: 9%; motor: <5%). **Ophthalmic**: Conjunctivitis (≤5%), increased lacrimation (1% to <5%). **Miscellaneous**: Fever (8%).
Monitoring Parameters	• Complete blood count • Renal and hepatic function. • Patients should be regularly monitored for acute tubular necrosis • Signs and symptoms of nephrogenic diabetes insipidus (e.g. hypernatraemia).
Drug Interactions	***Risk X: Avoid combination*** Abrocitinib, Baricitinib, BCG (Intravesical), Brivudine, Cladribine, Dengue Tetravalent Vaccine (Live), Deucravacitinib, Dipyrone, Etrasimod, Fexinidazole, Filgotinib, Mumps- Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Poliovirus Vaccine (Live/Trivalent/Oral), Ritlecitinib, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Taurursodiol, Tertomotide, Tofacitinib, Typhoid Vaccine, Upadacitinib, Vaccines (Live), Yellow Fever Vaccine. ***Risk D: Consider therapy modification:*** Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), Deferiprone, Denosumab, Ibuprofen, Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Methotrexate, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating).
Pregnancy and Lactation	**Pregnancy:** No human data. Animal studies have shown reproductive toxicity. Pemetrexed should not be used during pregnancy unless clearly necessary. Women of childbearing potential must use effective contraception during treatment with Pemetrexed and for 6 months following completion of treatment. Males are advised not to father a child during treatment and up to 3 months thereafter. **Lactation:** No data**.** Lactation must be discontinued during Pemetrexed therapy.
Administration	**Hazardous agent** (NIOSH 2016 [group 1]): Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. **IV infusion:** Infuse over 10 minutes on the first day of each 21-day cycle. **Combination treatments** • When used in combination with platinum-based therapy (Cisplatin or Carboplatin), administer Pemetrexed before the platinum. Patients should receive adequate antiemetic treatment and appropriate hydration prior to and/or after receiving treatment. • Administer pemetrexed after Pembrolizumab if administered on the same day.

	Preparation of administration: • Concentrate for Solution: Dilute the appropriate volume to 100 ml NS solution (0.9 %). • Powder for reconstitution: Reconstitute 100 mg vials with 4.2 ml and the 500 mg vials with 20 ml of NS (0.9%) solution for injection, without preservative, resulting in a solution containing 25 mg/ml pemetrexed. Gently swirl to dissolve. A colorless to yellow or green-yellow solution is formed. Further, dilute to 100ml NS solution. • Extravasation has been reported rarely and should be managed by local standard practice as with other non-vesicants. **N.B.** Refer to manufacturer PIL for specific considerations.
Emetogenicity	• **Low emetic risk:** (10%–30% frequency of emesis)
Warnings/ Precautions	• **Bone marrow suppression:** Pemetrexed may cause severe myelosuppression, including anemia, neutropenia, thrombocytopenia, and/or pancytopenia; myelosuppression is often dose-limiting. Severe myelosuppression may require blood transfusion or may lead to neutropenic infection. • Pemetrexed should not be given to patients until absolute neutrophil count (ANC) returns to ≥ 1500 cells/mm3 and platelet count returns to ≥ 100,000 cells/mm^3. Dose reductions for subsequent cycles are based on nadir ANC, platelet count, and maximum non-hematologic toxicity seen from the previous cycle. • **Mild to moderate renal insufficiency patients (45 to 79 ml/min)**: Avoid administration of NSAIDs 2-5 days before and 2 days after treatment with Pemetrexed. • **To reduce hematologic and non-hematologic toxicities**: Initiate Prophylactic folic acid supplements 1 week before the first dose of pemetrexed and continue daily for 21 days after the last pemetrexed dose. Administer vitamin B12, 1 mg IM injection, 1 week before the first dose and every 3 cycles. While to reduce skin adverse reactions administer dexamethasone 4 mg orally, twice daily the day before, the day of, and the day after Pemetrexed Injection administration. • **Cutaneous reactions:** Serious and occasionally fatal, bullous, blistering, and exfoliative dermatologic toxicity may occur; pretreatment with dexamethasone is necessary to reduce the incidence and severity of cutaneous reactions. Rarely, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. • **Hypersensitivity:** Hypersensitivity (including allergic reaction) has been reported with pemetrexed. • **Nephrotoxicity:** Pemetrexed may cause severe (and potentially fatal) kidney toxicity (monotherapy or in combination). Risk factors include dehydration, pre-existing hypertension or diabetes. Nephrogenic diabetes insipidus and

	renal tubular necrosis were also reported. Most of these events resolved after Pemetrexed withdrawal. Patients should be regularly monitored for acute tubular necrosis, decreased renal function, and signs and symptoms of nephrogenic diabetes insipidus (e.g. hypernatremia). • **Serious cardiovascular events**: including myocardial infarction and cerebrovascular events have been uncommonly reported during clinical studies with pemetrexed, usually when given in combination with another cytotoxic agent. Most of the patients in whom these events have been observed had pre-existing cardiovascular risk factors. • **Radiation pneumonitis:** have been reported in patients treated with radiation either prior, during or after their pemetrexed therapy. Caution with these patients and with the use of other radio sensitizing agents. • **Pulmonary toxicity:** Interstitial pneumonitis and Pulmonary embolism have been observed; may be serious and/or fatal. Signs/symptoms indicative of interstitial pneumonitis may include acute onset new or progressive pulmonary symptoms such as dyspnea, cough, or fever. • **Radiation recall:** Radiation recall may occur in patients administered pemetrexed who received radiation previously (weeks to years).
Storage and Light Sensitivity	• Store unopened vial at 2^0 C to 8^0 C. Do not freeze. • Infusion solutions can be stored for 72 hours at refrigerated temperature (2°C to 8°C). • Non-light sensitive. **N.B.** Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• This medicine lowers blood count. Avoid causes of bleeding and infection. Check blood counts regularly as told by the doctor. • Tell your doctor immediately if you have any renal, pulmonary, cardiovascular, or cutaneous symptoms. • This medicine is teratogenic and carcinogenic. • Talk with your doctor before taking any vaccinations.
Sequence of Administration	• Cell cycle specific. • Nonvesicants
Pharmaco-genomics	• Methylenetetrahydrofolate Reductase

B. Purine Analogues

1. Fludarabine

Generic name	Fludarabine
Dosage Form/Strengths	• Powder for Solution for I.V Infusion: 50mg • Concentrate for solution for injection/infusion: 50 mg/2 mL • Tablet 10mg.
Route of Administration	IV, Oral
Pharmacologic Category	Antimetabolite (Purine Analog), Antineoplastic agent. ATC Code: L01BB05.
Indications	**N.B.** *Refer to literature and specific protocols for all indications*. **Treatment of B-cell chronic lymphocytic leukemia (CLL) (refractory or progressive)** in adult patients who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-agent-containing regimen. **Other uses:** Waldenström Macroglobulinemia, Acute Myeloid Leukemia in adults.
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols.* **Adult Dosing** **IV:** 25 mg/m^2 over 30 minutes daily for five consecutive days every 28 days. Fludarabine may be administered till the achievement of the best response (usually 6 cycles). **Oral**: 40 mg/m^2 for 5 consecutive days every 28 days. **Pediatrics**: Safety and efficacy of Fludarabine in children below the age of 18 years have not been established.
Dosage Adjustment	**N.B.** Refer to the protocol used for specific dose modifications. **Dosing: Altered Kidney Function: Adult** **In chronic lymphocytic leukemia:** **IV** • CrCl 50 to 79 mL/minute: Reduce dose to 20 mg/m^2. • CrCl 30 to 49 mL/minute: Reduce dose to 15 mg/m^2. • CrCl <30 mL/minute: Use is contraindicated. **Oral** • CrCl 30 to 70 mL/minute: Reduce dose by up to 50%. • CrCl <30 mL/minute: Use is contraindicated. **Dosing: Hepatic Impairment: Adult** • There are no dosage adjustments. Caution. **Dosing: Adjustment for Toxicity: Adult** • Hematologic or nonhematologic toxicity (other than neurotoxicity): Consider treatment delay or dosage reduction. Patients with bone

	marrow impairment may require dosage reductions. • Hemolysis: Discontinue treatment (corticosteroids may or may not effectively control hemolytic episodes). • Neurotoxicity: Consider treatment delay or discontinuation.
Contra-indications	• Hypersensitivity reactions to Fludarabine or any components of the formulation. • Renal impaired patients with a creatinine clearance of less than 30 ml/minute. • In patients with decompensated hemolytic anemia.
Adverse Drug Reactions	**Bone marrow suppression.** **Autoimmune effects.** **Neurotoxicity.** **>10%** **Cardiovascular**: Edema (8% to 19%). **Central nervous system**: Fatigue (10% to 38%), neurological signs and symptoms (doses >96 mg/m^2 /day for 5 to 7 days: 36%; doses <125 mg/m^2/cycle: <1%; characterized by cortical blindness, coma, and paralysis; symptom onset may be delayed for 3 to 4 weeks), pain (20% to 22%), chills (11% to 19%), paresthesia (4% to 12%). **Dermatologic**: Skin rash (15%), diaphoresis (1% to 13%). **Gastrointestinal**: Nausea and vomiting (31% to 36%), anorexia (7% to 34%), diarrhea (13% to 15%), gastrointestinal hemorrhage (3% to 13%). **Genitourinary**: Urinary tract infection (2% to 15%). **Hematologic & oncologic**: Anemia (60%), neutropenia (grade 4: 59%; nadir: ~13 days), thrombocytopenia (55%; nadir: ~16 days), bone marrow depression (nadir: 10 to 14 days; recovery: 5 to 7 weeks; dose-limiting toxicity). **Infection**: Infection (33% to 44%). **Neuromuscular & skeletal**: Asthenia (9% to 65%), myalgia (4% to 16%). **Ophthalmic**: Visual disturbance (3% to 15%). **Respiratory**: Cough (10% to 44%), pneumonia (16% to 22%), dyspnea (9% to 22%), upper respiratory tract infection (2% to 16%). **Miscellaneous**: Fever (60% to 69%). **1% to 10%** **Cardiovascular**: Angina pectoris (≤6%), cardiac arrhythmia (≤3%), cardiac failure (≤3%), cerebrovascular accident (≤3%), myocardial infarction (≤3%), supraventricular tachycardia (≤3%), deep vein thrombosis (1% to 3%), phlebitis (1% to 3%), aneurysm (≤1%), transient ischemic attacks (≤1%). **Central nervous system**: Malaise (6% to 8%), headache (≤3%), sleep disorder (1% to 3%), cerebellar syndrome (≤1%), depression (≤1%), difficulty thinking (≤1%). **Dermatologic**: Alopecia (≤3%), pruritus (1% to 3%), seborrhea (≤1%) **Endocrine & metabolic**: Hyperglycemia (1% to 6%), dehydration (≤1%). **Gastrointestinal**: Stomatitis (≤9%), cholelithiasis (≤3%), esophagitis (≤3%),

	constipation (1% to 3%), mucositis (≤2%), dysphagia (≤1%). **Genitourinary**: Dysuria (3% to 4%), urinary hesitancy (≤3%), hematuria (2% to 3%), proteinuria (≤1%). **Hematologic & oncologic**: Hemorrhage (≤1%), tumor lysis syndrome (≤1%). **Hepatic**: Abnormal hepatic function tests (1% to 3%), hepatic failure (≤1%). **Hypersensitivity**: Anaphylaxis (≤1%). **Neuromuscular & skeletal**: Osteoporosis (≤2%), arthralgia (≤1%). **Otic**: Hearing loss (2% to 6%). **Renal**: Renal failure (≤1%), renal function test abnormality (≤1%). **Respiratory**: Pharyngitis (≤9%), hypersensitivity pneumonitis (≤6%), hemoptysis (1% to 6%), sinusitis (≤5%), bronchitis (≤1%), epistaxis (≤1%), hypoxia (≤1%).
Monitoring Parameters	• CBC with differential and platelet count • Liver function test • Kidney function test • Serum uric acid. • Monitor signs and symptoms of hemolysis, infection, neurotoxicity, and progressive multifocal leukopathy. • Monitor patients with bone marrow impairment or renal impairment closely for excess toxicity.
Drug Interactions	***Risk X: Avoid combination:*** Abrocitinib, Baricitinib, BCG (Intravesical), Cladribine, Deucravacitinib, Fexinidazole, Filgotinib, Mumps- Rubella- or Varicella-Containing Live Vaccines, Natalizumab, Pentostatin, Pimecrolimus, Poliovirus Vaccine, Tertomotide, Upadacitinib, Yellow Fever Vaccine. ***Risk D: Consider therapy modification*** Coccidioides immitis Skin Test, COVID-19 Vaccine, Deferiprone, Denosumab, Influenza Virus Vaccines, Leflunomide, Lenograstim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Immunosuppressants.
Pregnancy and Lactation	**Pregnancy:** Avoid. Fludarabine can cause fetal harm when administered to a pregnant woman. Women should be advised to avoid becoming pregnant. Patients are advised to use effective contraceptive measures during and at least for 6 months after cessation of therapy. **Lactation:** Avoid due to the potential for serious adverse reactions including tumorigenicity in nursing infants.
Administration	**Hazardous agent** (NIOSH 2016 [group 1]): Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. **Administration: IV** Powder is to be made up in 2 ml water for injection. • **IV bolus injection**: Further dilute in 10 ml sodium chloride (0.9%). • **Infusion**: Dose may be diluted in 100 ml sodium chloride (0.9%) and infused over approximately 30 minutes

	Administration: Oral: Tablet may be administered with or without food; should be swallowed whole with water; do not chew, break, or crush. **N.B.** Refer to manufacturer PIL for specific considerations.
Emetogenicity	• **IV**: Minimal (<10%). • **Oral**: Minimal to low (<30%).
Warnings/ Precautions	**Neurologic Toxicities (Dose-Dependent):** • Dose levels (96 mg/m^2/day for 5 to 7 days) approximately 4 times greater than that recommended for CLL (25 mg/m^2/day for 5 days) were associated with a syndrome characterized by delayed blindness, coma, and death. • Other severe central nervous system toxicity, including coma, seizures, agitation, and confusion, has been reported in patients treated at doses for chronic lymphocytic leukemia. **Bone Marrow Suppression:** • Severe bone marrow suppression, notably anemia, thrombocytopenia, and neutropenia, has been reported. Cumulative myelosuppression may be seen. Monitor closely • Several instances of trilineage bone marrow hypoplasia or aplasia resulting in pancytopenia, sometimes resulting in death, have been reported in adult patients. • May consider Methotrexate/ Trimethoprim and continuing up to 6 months after treatment as prophylactic against Pneumocystis jirovecii pneumonia (PJP) (consider patient-specific risk factors). **Autoimmune Reactions:** • Life-threatening autoimmune phenomena have been reported to occur during or after treatment with Fludara such as hemolytic anemia and acquired hemophilia. • Discontinue Fludara in case of hemolysis. Blood transfusion and adrenocorticoid preparations are the most common treatment measures for autoimmune hemolytic anemia. Do not challenge another time. **Transfusion Associated Graft-Versus-Host Disease:** • Transfusion-associated graft-versus-host disease has been observed after transfusion of non-irradiated blood in Fludarabine-treated patients. Fatal outcomes consequently have been reported with high frequency. If needed, transfuse irradiated blood only to fludarabine-treated patients. **Renal Impairment:** • Adjust doses for renal impairment. Monitor closely for excessive toxicity. • Use is contraindicated in patients with creatinine clearance less than 30 mL/min. **Vaccination:** • During and after treatment with fludarabine Injection, vaccination with live

	vaccines should be avoided. **Skin toxicity**: • Primarily skin rashes. Worsening or flare-up of pre-existing skin cancer lesions, as well as new onset of skin cancer, has been reported during or after treatment with fludarabine.
Storage and Light Sensitivity	**IV** • Store intact vials at (2°C – 8°C) or at (15°C -30°C). Refer to the product label. • Protect from light. • **Powder**: Stability after reconstitution in sterile conditions has been demonstrated for 7 days at 4 °C. • **Concentrate**: After dilution, 28 days when stored in a refrigerator (2°C - 8°C) with protection from light. **Oral** Store at 15°C to 30°C; should be kept within packaging until use. **N.B.** Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• This medication may lower blood counts. Avoid causes of infection and bleeding. • Avoid driving and doing other tasks or actions that call for you to be alert or have clear eyesight until you see how this drug affects you. • Talk with your doctor before getting any vaccines while you take this drug and after you stop taking it. • Tell your doctor If you have ever had an autoimmune disease. • Call your doctor immediately if you have a seizure, change in eyesight, or you feel agitated or confused; Signs of lung or breathing problems; Change in color or size of a mole, skin lump or a severe skin reaction, or urination disorders.
Sequence of Administration	• Cell cycle specific. • Non-vesicant. • When combined with Cytarabine, Fludarabine should be given first for enhanced efficacy.

2. Mercaptopurine

Generic name	Mercaptopurine
Dosage Form/Strengths	Tablets 50 mg
Route of Administration	Oral
Pharmacologic Category	Antimetabolite (Purine Analog); Antineoplastic Agent, Immunosuppressant Agent. ATC Code: L01BB02
Indications	**N.B.** *Refer to literature and specific protocols for all indications*. • Acute lymphoblastic leukemia. • Acute promyelocytic leukemia (Acute myeloid leukemia M3).
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols.* • **Adult and pediatric dosing** **Oral**: 1.5 to 2.5 mg/kg once daily (50 to 75 mg/m^2 once daily). Adjust dose based on blood counts and the used protocol. Patients with reduced or absent activity of Thiopurine Methyl Transferase (TPMT) enzyme or nucleotide diphosphatase (NUDT15): Starting or target doses should be lower to avoid severe myelosuppression.
Dosage Adjustment	**N.B.** Refer to the protocol used for specific dose modifications. • **Dosing: Altered Kidney Function: Adult and pediatrics** – CrCl ≥50 mL/minute: There are no dosage adjustments needed. – CrCl <50 mL/minute: Initiate with the lowest recommended starting dose or increase the dosing interval to every 36 to 48 hours. Adjust the dose to maintain desirable neutrophil counts. • **Dosing: Hepatic Impairment: Adult and pediatrics** ○ Hepatic impairment at baseline: Initiate with the lowest recommended starting dose; adjust the dose to maintain desirable ANC level. ○ Hepatotoxicity during treatment: Withhold therapy.
Contra-indications	• Hypersensitivity to mercaptopurine or any component of the formulation.
Adverse Drug Reactions	**Myelosuppression** **Hepatotoxicity** **Immunosuppression** **Treatment-related malignancies** **Macrophage activation syndrome** **>10%** **Dermatologic**: Skin rash (5% to 20%). **Gastrointestinal**: Anorexia (5% to 20%), diarrhea (5% to 20%), nausea (5% to 20%), vomiting (5% to 20%).

	Hematologic & oncologic: Bone marrow depression (dose-related: >20%, including anemia, neutropenia, lymphocytopenia, and thrombocytopenia). **Nervous system**: Malaise (5% to 20%). **1% to 10%** **Dermatologic**: Hyperpigmentation (<5%), urticaria (<5%). **Endocrine & metabolic**: Hyperuricemia (<5%). **Gastrointestinal**: Oral lesion (<5%), pancreatitis (<5%). **Hepatic**: Hyperbilirubinemia (<5%), increased serum transaminases (<5%). **Infection**: Infection (<5%). **Frequency not defined** **Dermatologic**: Alopecia. **Gastrointestinal**: Cholestasis, sprue-like symptoms, stomach pain, stomatitis, ulcerative bowel lesion. **Genitourinary**: Oligospermia, renal toxicity. **Hematologic & o**ncologic: Granulocytopenia, leukopenia, metastases **Hepatic**: Ascites, hepatic encephalopathy, hepatic fibrosis, hepatic injury, hepatic necrosis, hepatomegaly, hepatotoxicity, intrahepatic cholestasis, jaundice, toxic hepatitis. **Immunologic**: Immunosuppression. **Nervous** system: Drug fever. **Respiratory**: Pulmonary fibrosis.
Monitoring Parameters	• CBC with differential. • Liver function test (transaminases, alkaline phosphatase, and bilirubin) at weekly intervals at the beginning and monthly intervals thereafter. • Renal function test. • Uric acid levels. • Consider TPMT and NUDT15 genotypes evaluation.
Drug Interactions	***Risk X: Avoid combination:*** Abrocitinib, Azathioprine, Baricitinib, BCG (Intravesical), Brivudine, Cladribine, Dengue Tetravalent, Vaccine (Live), Deucravacitinib, Dipyrone, Febuxostat, Fexinidazole, Filgotinib, Mumps- Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Poliovirus Vaccine (Live/Trivalent/Oral), Ribavirin, Ritlecitinib, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene, Laherparepvec, Tertomotide, Tofacitinib, Typhoid Vaccine, Upadacitinib, Vaccines (Live), Yellow Fever Vaccine. ***Risk D: Consider therapy modification*** Allopurinol, Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), Deferiprone, Denosumab, Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Methotrexate, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-TVaccines (Inactivated/Non-Replicating). **Notes**

	Allopurinol decreases the rate of catabolism of Mercaptopurine. So, when administered concomitantly, administer only 25 % of the usual dose of 6-Mercaptopurine to avoid severe toxicity. ○ Inhibition of the anticoagulant effect of Warfarin, when given with Mercaptopurine, has been reported. Monitor INR. ○ Enhanced marrow suppression has been noted in some patients also receiving Trimethoprim-sulfamethoxazole. Methotrexate increases the bioavailability of 6-MP by inhibiting xanthine oxidase, which catabolizes 6-MP. Methotrexate (20 mg/m^2 orally) increased 6-Mercaptopurine AUC by approximately 31% and methotrexate (2 or 5 g/m^2 IV) increased 6-mercaptopurine AUC by 69 and 93%, respectively. Adjust dose and monitor CBC closely.
Pregnancy and Lactation	**Pregnancy:** Avoid. Mercaptopurine can cause fetal harm when administered to a pregnant woman. Miscarriage and stillbirth have been reported after use in the first trimester. Advise patients of reproductive potential to use effective contraception during treatment and for 6 months after the last dose for females and 3 months for males. **Lactation**: Not recommended due to the potential of serious adverse reactions in nursing infants, women should discontinue breastfeeding during therapy.
Administration	**Hazardous agent** (NIOSH 2016 [group 1]): Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. **Administration: Oral** Administer at the same time each day, consistently with or without food preferably on an empty stomach; avoid concomitant milk products. If a patient misses a dose, instruct the patient to continue with the next scheduled dose. **N.B.** Refer to manufacturer PIL for specific considerations.
Emetogenicity	• Minimal to low (<30%)
Warnings/ Precautions	**Bone marrow suppression**: • Dose-related leukopenia, thrombocytopenia, and anemia are common. • Monitor blood counts. Adjust dose when needed. Bone marrow suppression is reversible if 6-mercaptopurine is withdrawn early enough. **Hepatotoxicity:** • Hepatotoxicity has been reported, including jaundice, ascites, hepatic necrosis (may be fatal) and Hepatic encephalopathy. • Monitor liver function tests weekly with treatment initiation, then monthly thereafter. Monitor more frequently in those with preexisting liver disease or receiving other potentially hepatotoxic therapy. • Reduce initial dose in patients with baseline hepatic impairment; monitor closely for toxicity. Withhold treatment at the onset of hepatotoxicity, or for clinical signs of jaundice (hepatomegaly, anorexia,

tenderness).

Immunosuppression:

Mercaptopurine is immunosuppressive; immune responses to infections may be impaired and the risk for infection is increased. Immunization with live organism vaccines is not recommended.

Macrophage Activation Syndrome:

Macrophage Activation Syndrome (MAS) is a life-threatening disorder which may develop in patients with autoimmune disorders (particularly inflammatory bowel disease); Mercaptopurine use for the treatment of autoimmune conditions (unapproved use) may cause increased susceptibility to MAS. Discontinue Mercaptopurine if MAS develops or is suspected. Monitor: promptly treat infections such as Epstein-Barr virus (EBV) and cytomegalovirus (which are known triggers for MAS).

Metabolism and nutrition disorders:

Administration of purine analogues, Azathioprine and Mercaptopurine, may interfere with the niacin pathway, potentially leading to nicotinic acid deficiency (pellagra). It's marked by dementia, diarrhea, and dermatitis. Appropriate medical care with niacin/nicotinamide supplementation must be initiated, and dose reduction or discontinuation of Azathioprine must be considered.

Secondary malignancy:

- Immunosuppressive agents, including mercaptopurine, are associated with the development of lymphoproliferative disorders and other malignancies, notably skin cancers, sarcomas and uterine cervical cancer in situ.
- Discontinuation of immunosuppression may provide partial regression of the lymphoproliferative disorder.

Renal impairment:

- Reduce initial dose or extend dosing interval in patients with renal impairment (CrCl <50 mL/minute).
- Hydration, urine alkalization, and prophylactic anti hyperuricemic therapy such as Allopurinol may minimize potential renal complications. The dosage of Mercaptopurine should be reduced to one-third to one-quarter of the usual dose if Allopurinol is given concurrently.

TPMT or NUDT15 deficiency:

- Patients with thiopurine S-methyltransferase (TPMT) or nucleotide diphosphatase (NUDT15) deficiency may be at a higher risk for developing thiopurine toxicity, especially severe myelosuppression and may require dose reductions of thiopurine (e.g., mercaptopurine, azathioprine, thioguanine).

Photosensitivity has been reported with Mercaptopurine: Minimize sun exposure.

	Hypoglycemia: has been reported in children.
Storage and Light Sensitivity	• Keep at room temperature between 15°C and 30°C. • Protect from light. Keep the bottle tightly closed. **N.B.** Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• This drug induces low blood cell counts. Avoid infections and bleeding causes. • Talk with your doctor before getting any vaccines or other medications. • Call a doctor if you have any of these symptoms: signs of infection, signs of kidney problems like unable to pass urine, liver problems like dark urine and yellow skin or eyes, diarrhea, or dermatitis. • This drug may cause harm to an unborn baby or the loss of an unborn baby. Avoid use in pregnant women.
Sequence of Administration	**NUDT15 – Mercaptopurine:** • Patients with inherited mutated NUDT15 gene are at increased risk for severe 6- mercaptopurine toxicity. • Patients with homozygous NUDT15 deficiency (i.e., poor metabolizers]) require substantial dosage reductions. In any case, close monitoring of blood counts is necessary. **TPMT-deficient patients:** • 6-Mercaptopurine is metabolized by the thiopurine polymorphic S-methyltransferase TPMT enzyme. Patients with little or no inherited (TPMT) activity are at increased risk for severe 6- 6-mercaptopurine toxicity from conventional doses of 6-mercaptopurine and generally require substantial dose reduction. Consider testing. TPMT testing cannot substitute for hematological monitoring in patients receiving mercaptopurine.

3. Thioguanine

Generic name	Thioguanine (Tioguanine)
Dosage Form/ Strengths	Tablet: 40mg.
Route of Administration	Oral
Pharmacologic Category	Antineoplastic Agent, Antimetabolite (Purine Analog). ATC Code: L01BB03
Indications	**N.B**. Refer to literature and specific protocols for all indications. • **Acute leukemia**: Acute myelogenous leukemia and acute lymphoblastic leukemia. **N.B.** Thioguanine can be used in stages (induction, remission, or consolidation) while not recommended for use during maintenance therapy or long-term treatments due to the high risk of hepatotoxicity.
Dosage Regimen	**N.B.** Different doses and regimens have been used; consult the literature for specific protocols. **Adult and pediatric dosing** • Weight-based dosing: Oral: 2 mg/kg once daily for 4 weeks; may be increased to 3mg/kg daily cautiously if no clinical improvement after 4 weeks and ANC and platelet counts are not depressed. • Surface area-based dosing: 100 to 200 mg/m^2 per day.
Dosage Adjustment	**N.B**. Refer to the protocol used for specific dose modifications. • **Dosing: Altered Kidney Function: Adult and pediatric** There is no dose adjustment needed. • **Dosing: Hepatic Impairment: Adult and pediatric** There are no available dosage adjustment recommendations. Monitor liver functions more frequently in patients with pre-existing liver disease. • **Hepatotoxicity or Hematological toxicity during treatment**: Discontinue Thioguanine in patients with evidence of toxicity. Toxicities have been reported to be reversible upon withdrawal. • **Dosage adjustment for thiopurine S-methyltransferase (TPMT) or NUDT15 deficiency or mutation patients** These patients are at increased risk for severe toxicity from conventional doses of Tioguanine. Homozygous deficient patients of either TMPT or NUDT15 require dose reduction. While most heterozygous patients may tolerate recommended doses but some may require dose reduction. - Heterozygous for either TPMT or NUDT15: administer 50-90% of the planned dose.

	- Heterozygous for both TPMT and NUDT15: administer 30-50% of the planned dose. - Homozygous for either TPMT or NUDT15: administer 5-10%. - Adjust dose based on the degree of myelosuppression and condition being treated.
Contra-indications	• Hypersensitivity to Thioguanine or any component of the formulation. • Prior resistance to Thioguanine (or Mercaptopurine).
Adverse Drug Reactions	• **Myelosuppression** • **Hyperuricemia** • **Hepatic Effects** **Frequency not defined:** **Cardiovascular**: Esophageal varices, portal hypertension. **Endocrine & metabolic**: Fluid retention, hyperuricemia (common), increased gamma-glutamyl transferase, weight gain. **Gastrointestinal**: Anorexia, intestinal necrosis, intestinal perforation, nausea, stomatitis, vomiting. **Hematologic and oncologic**: Anemia (may be delayed), bone marrow depression, granulocytopenia, hemorrhage, leukopenia (common; may be delayed), pancytopenia, splenomegaly, thrombocytopenia (common; may be delayed). **Hepatic**: Ascites, hepatic disease (hepatoportal sclerosis), hepatic focal nodular hyperplasia (regenerative), hepatic necrosis (centrilobular), hepatic sinusoidal obstruction syndrome, hepatomegaly (tender), hepatotoxicity, hyperbilirubinemia, increased liver enzymes, increased serum alkaline phosphatase, jaundice, peliosis hepatitis, periportal fibrosis. **Infection**: Infection. **Neuromuscular & skeletal**: Bone hypoplasia.
Monitoring Parameters	• CBC with differential (Total Leucocyte Count, neutrophils, and platelets). • Liver function test weekly (transaminases, alkaline phosphatase, and bilirubin) • Monitor for signs/symptoms of hepatotoxicity, portal hypertension (splenomegaly, esophageal varices, thrombocytopenia), or sinusoidal obstruction syndrome (veno-occlusive disease; fluid retention, ascites, hepatomegaly with tenderness, or hyperbilirubinemia); infection, or bleeding. • TPMT genotyping or phenotyping may assist in identifying patients at risk for developing toxicity. • Consider genotyping for NUDT15 deficiency in patients who experience severe bone marrow toxicities or repeated myelosuppressive episodes.
Drug Interactions	***Risk X: Avoid combination*** Baricitinib, BCG (Intravesical), Brivudine, Cladribine, Dengue Tetravalent

	Vaccine (Live), Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Mumps-Rubella- or Varicella-Containing Live Vaccines, Nadofaragene, Firadenovec, Natalizumab, Pimecrolimus Poliovirus Vaccine (Live/Trivalent/Oral), Ritlecitinib, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide Immunosuppressants, Tofacitinib Immunosuppressants, Typhoid Vaccine, Upadacitinib, Vaccines (Live), Yellow Fever Vaccine. ***Risk D: Consider therapy modification*** Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), Deferiprone, Denosumab, Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating). **Notes** Bone marrow suppression could be exacerbated by coadministration with drugs that inhibit TPMT, such as Olsalazine, Mesalazine, or Sulphasalazine.
Pregnancy and Lactation	**Pregnancy**: Avoid use whenever possible during pregnancy, particularly during the first trimester. Based on data from animal reproduction studies, exposure to Thioguanine may cause fetal harm. **Lactation**: Due to the risk of serious adverse reactions in nursing infants, women should discontinue breast-feeding during therapy.
Administration	**Hazardous agent** (NIOSH 2016 [group 1]): Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. **Administration**: **Oral** Administer orally; total daily dose can be administered at one time. **N.B.** Refer to manufacturer PIL for specific considerations.
Emetogenicity	Minimal or low (<30%)
Warnings/ Precautions	**Bone marrow suppression** • Myelosuppression (anemia, leukopenia, and/or thrombocytopenia) is a common dose-related toxicity (may be delayed). Patients with genetic enzyme deficiency of thiopurine methyltransferase (TPMT) or nudix hydrolase (NUDT15) may be highly sensitive to myelosuppressive effects and may require substantial dose reductions. • The leucocyte and platelet counts continue to fall after treatment is stopped, so at the first sign of an abnormally large fall in these counts, treatment should be temporarily discontinued. **Hepatotoxicity** • Long-term continuous therapy or maintenance treatment is associated with a high risk for hepatotoxicity. Hepatotoxicity may be more

	prevalent in male patients. • Liver toxicity usually presents with signs of portal hypertension (splenomegaly, thrombocytopenia, and esophageal varices) and as hepatic veno-occlusive disease (hyperbilirubinemia, tender hepatomegaly, weight gain due to fluid retention, and ascites). Elevations of liver enzymes have also been reported in association with liver toxicity but do not always occur. • Reversal of signs and symptoms of this liver toxicity has been reported upon withdrawal of short-term or long-term continuous therapy. **Photosensitivity** Thioguanine may cause photosensitivity; sunscreen and protective clothing are recommended. **Secondary malignancies** Thioguanine is potentially carcinogenic. **Cross-resistance** Cross-resistance with Mercaptopurine generally occurs. **Vaccines** Avoid vaccination with live vaccines during treatment.
Storage and Light Sensitivity	• Store between 15°C and 30°C. Store in a dry place. • Protect from light. **N.B**. Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• This medicine lowers blood count. Avoid causes of infection and bleeding. • You may get sunburned more easily. Use sunscreen and wear clothing and eyewear that protects you from the sun. • Talk to your doctor before receiving any vaccines. • Tell your doctor immediately if there are any signs of infection or liver problems like dark urine, tiredness, decreased appetite or yellow skin or eye. • Tell your doctor if you have been tested for thiopurine S-methyltransferase (TPMT) or nucleotide diphosphatase (NUDT15) deficiency. The chance of blood or bone marrow problems may be raised if you have TPMT or NUDT15 deficiency. If you have questions, talk with your doctor. • If you miss a dose of thioguanine, take it as soon as you can if it is within 12 hours of the missed dose. If it is over 12 hours since your missed dose, skip the missed dose and go back to your usual dosing times. • If you have an upset stomach, throwing up, diarrhea, or decreased appetite, talk with your doctor. There may be ways to lower these side effects.
Pharmaco-genomics	• **Thiopurine S-methyltransferase (TPMT):** Gene Testing Recommended. • **Nudix hydrolase (NUDT15):** Gene Testing May Be Considered Patients with mutations or poor metabolizers of NUDT15 or TPMT are at increased risk for severe toxicity from conventional doses of Tioguanine. Refer to

	dosage adjustments.

C. Pyrimidine analogues

1. Azacitidine

Generic Name	Azacitidine
Dosage Form/ Strengths	Lyophilized powder for suspension for SC injection: 100mg. Lyophilized powder for suspension for SC or IV injection: 100mg.
Route of Administration	Subcutaneous, Intravenous
Pharmacologic Category	Antimetabolite; Antineoplastic Agent, DNA Methylation Inhibitor. ATC Code: L01BC07
Indications	**N.B.** Refer to literature and specific protocols for all indications. Treatment of adult patients who are not eligible for hematopoietic stem cell transplantation (HSCT) with: • Intermediate-2 and high-risk myelodysplastic syndromes (MDS). • Chronic myelomonocytic leukemia (CMML) • Acute myeloid leukemia (AML).
Dosage Regimen	**N.B.** Different doses and regimens have been used; consult the literature for specific protocols. • SC or IV infusion: Initial: 75 mg/m^2 daily for 7 days. This is the recommended dose for all patients regardless of baseline hematology values. • Repeat cycles every 4 weeks. After 2 cycles, may increase dose to 100 mg/m^2 if no beneficial effect is seen and no toxicity other than nausea and vomiting has occurred. Patients should be treated for a minimum of 4 to 6 cycles. Continue treatment as long as the patient continues to benefit.
Dosage Adjustment	**N.B.** Refer to the protocol used for specific dose modifications. **Dosage: Renal Impairment** • No initial dose adjustments are required. • Monitor carefully for toxicity as Azacitidine and its metabolites are primarily excreted by the kidneys. • **BUN or serum creatinine,** unexplained elevations to ≥ 2-fold: Delay next cycle until values return to normal or baseline and reduce dose by 50% on the next course. **Dosing: Hepatic Impairment** • No initial dose adjustments are required. No studies. • Monitor carefully for toxicity. Adjust subsequent doses based on hematology laboratory values. • Azacitidine is contraindicated in patients with advanced malignant hepatic tumors.

Dosage Adjustment due to electrolyte imbalance

Serum bicarbonate levels, unexplained reductions to less than 20 mEq/L: Reduce dose by 50% on the next course.

Dose adjustment due to hematological toxicity

- **Patients without reduced baseline blood counts** (i.e. White Blood Cells (WBC) ≥ 3.0 x 10^9 /l and ANC ≥ 1.5 x 10^9 /l, and platelets ≥ 75.0 x 10^9 /l) prior to the first treatment:
  - If hematological toxicity is observed, delay next cycle until recovery.
  - If recovered within 14 days, no dose modifications are needed.
  - If not recovered with 14 days, follow the dose adjustments table:

Nadir ANC (x 10^9 /l)	Nadir Platelets (x 10^9 /l)	Dose in the next cycle if recovery is not achieved within 14 days (%)
≤ 1.0	≤ 50.0	50 %
> 1.0	> 50.0	100 %

- **Patients with reduced baseline blood counts** (i.e. WBC < 3.0 x 10^9 /l or ANC < 1.5 x 10^9 /l or platelets < 75.0 x 10^9 /l) prior to the first treatment:
  - If the decrease in WBC or ANC or platelets is > 50 % from that before treatment, with no improvement in cell line differentiation, delay the next cycle until recovery.
  - If recovered within 14 days, no dose modifications are needed.
  - If not recovered within 14 days, no dose adjustments should be made if the bone marrow cellularity is > 50 %. However, if bone marrow cellularity is ≤ 50 %, treatment should be delayed, and the dose reduced according to the following table:

Bone marrow cellularity	Dose in the next cycle, if recovery is not achieved within 14 days (%)	
	Recovery ≤ 21 days	Recovery > 21 days
15-50 %	100 %	% 50 %
< 15 %	100 %	33 %

Contra-indications

- Hypersensitivity to Azacitidine or any component of the formulation.
- Advanced malignant hepatic tumors.
- Breast-feeding.

Adverse Drug Reactions

>10%

Cardiovascular: Chest pain (16%)

Dermatologic: Ecchymoses (31%), erythema of skin (7% to 17%), pruritus (12%), skin rash (10% to 14%)
Gastrointestinal: Abdominal pain (13% to 22%), abdominal tenderness (12%), anorexia (21%), constipation (34% to 50%), decreased appetite (13%), diarrhea (36% to 50%; grades 3/4: 5%), nausea (48% to 71%; grades 3/4: 2% to 3%), vomiting (27% to 60%; grades 3/4: 3%)
Hematologic & oncologic: Anemia (25% to 70%; grades 3/4: 4% to 14%), febrile neutropenia (7% to 16%; grades 3/4: 11% to 13%), leukopenia (18% to 48%; grades 3/4: 15%), neutropenia (32% to 74%; grades 3/4: 49% to 61%), petechia (11% to 24%; more common with IV administration), thrombocytopenia (65% to 70%; grades 3/4: 21% to 58%)
Local: Bruising at injection site (5% to 14%), erythema at injection site (35% to 43%), injection-site reaction (14% to 29%), pain at injection site (19% to 23%)
Nervous system: Anxiety (5% to 13%), asthenia (≤44%), dizziness (11% to 19%), fatigue (≤44%), headache (22%), insomnia (9% to 11%), malaise (11%)
Neuromuscular & skeletal: Arthralgia (14% to 22%), limb pain (11%), myalgia (16%)
Respiratory: Dyspnea (5% to 29%), nasopharyngitis (15%), pneumonia (8% to 27%), upper respiratory infection (9% to 13%)
Miscellaneous: Fever (30% to 52%)
1% to 10%
Cardiovascular: Atrial fibrillation (<5%), chest wall pain (5%), congestive cardiomyopathy (<5%), heart failure (<5%), hypertension (9%), hypotension (7%), orthostatic hypotension (<5%), septic shock (<5%)
Dermatologic: Cellulitis (<5%), cutaneous nodule (5%), pruritic rash (<5%), pyoderma gangrenosum (<5%), skin sclerosis (<5%), urticaria (6%), xeroderma (5%)
Endocrine & metabolic: Dehydration (<5%), hypokalemia (6%; more common with IV administration), weight loss (4% to 8%)
Gastrointestinal: Abscess of rectum and/or peri-rectal area (<5%), cholecystectomy (<5%), cholecystitis (<5%), diverticulitis of the gastrointestinal tract (<5%), dyspepsia (6%), gastrointestinal hemorrhage (<5%), gingival hemorrhage (10%), loose stools (6%), melena (<5%), oral hemorrhage (5%), stomatitis (8%)
Genitourinary: Hematuria (6%), urinary tract infection (9%)
Hematologic & oncologic: Agranulocytosis (<5%), bone marrow failure (<5%), hematoma (9%), leukemia cutis (<5%), pancytopenia (<5%), postprocedural hemorrhage (6%), splenomegaly (<5%)
Hypersensitivity: Anaphylactic shock (<5%), hypersensitivity reaction (<5%)
Infection: Bacterial infection (<5%), blastomycosis (<5%), Klebsiella pneumoniae infection (<5%), limb abscess (<5%), neutropenic sepsis (<5%), sepsis (<5%, including Klebsiella sepsis), staphylococcal bacteremia (<5%), staphylococcal infection (<5%), systemic inflammatory response syndrome (<5%), toxoplasmosis (<5%)
Local: Hematoma at injection site (6%), induration at injection site (5%), injection-site granuloma (5%), injection-site infection (<5%), injection-site pruritus (7%), rash at

	injection site (6%), skin discoloration at injection site (5%), swelling at injection site (5%) **Nervous system**: Cerebral hemorrhage (<5%), debility (<5%), intracranial hemorrhage (<5%), lethargy (7% to 8%), myasthenia (<5%), seizure (<5%) **Neuromuscular & skeletal**: Aggravated bone pain (<5%), neck pain (<5%) **Ophthalmic**: Subconjunctival hemorrhage (<5%) **Renal**: Flank pain (<5%), renal failure syndrome (<5%) **Respiratory**: Hemoptysis (<5%), pharyngolaryngeal pain (6%), pneumonitis (<5%), pulmonary infiltrates (<5%), respiratory distress (<5%), rhinitis (6%), streptococcal pharyngitis (<5%)
Monitoring Parameters	• CBC with differential and platelets at baseline and before each cycle. • Renal function at baseline and before each cycle. • Liver function tests. • Electrolytes (serum bicarbonate). • Consider cardiopulmonary assessment prior and during treatment.
Drug Interactions	***Risk X: Avoid combination:*** Abrocitinib, Baricitinib, BCG Products, Brivudine, Cedazuridine, Chikungunya Vaccine (Live), Chloramphenicol (Systemic), Cladribine, Dengue Tetravalent Vaccine (Live), Deucravacitinib, Dipyrone, Etrasimod, Fexinidazole, Filgotinib, Mumps- Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Poliovirus Vaccine (Live/Trivalent/Oral), Ritlecitinib, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec. Tertomotide. Tofacitinib, Typhoid Vaccine, Upadacitinib, Vaccines (Live), Yellow Fever Vaccine. ***Risk D: Consider therapy modification:*** Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), Deferiprone, Denosumab, Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating).
Pregnancy and Lactation	**Pregnancy:** Avoid. No human data. Azacitidine was teratogenic and caused embryo-fetal lethality in animals at doses lower than the recommended human daily dose. Use effective contraception during and up to 3 months after treatment. Azacitidine may impair male fertility. **Lactation**: Due to the potential for serious adverse reactions in nursing infants, not recommended during treatment with Azacitidine and for 1 week after the last dose.
Administration	**Hazardous Agent**: Probably Carcinogenic to Humans. Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. If Azacitidine suspension comes in contact with the skin, immediately wash with soap and water; if it comes into contact with mucous membranes, flush thoroughly with water. **Preparation for administration:** **Subcutaneous:**

	• Reconstitute slowly with 4 mL sterile water for injection. Vigorously shake or roll the vial until a uniform suspension is achieved. The suspension will be cloudy. The resulting suspension will contain Azacitidine 100 mg/4mL. Do not filter the suspension after reconstitution. Doing so could remove the active substance. • The shelf life of the reconstituted medicinal product can be extended by reconstituting it with refrigerated (2 °C to 8 °C) water for injections. **Intravenous:** • Reconstitute with 10 ml sterile water for injection. Vigorously shake or roll the vial until a clear solution. The resulting solution will contain Azacitidine 10 mg/mL. • Withdraw the required amount to deliver the desired dose and inject into a 50-100 mL infusion solution of either 0.9% Sodium Chloride Injection or Lactated Ringer's Injection. • Intravenous Incompatibility with 5% Dextrose solutions, or solutions that contain bicarbonate. **Administration: Subcutaneous:** • Allow refrigerated suspensions to come to room temperature (for up to 30 minutes) prior to administration. • Reconstituted Azacitidine should be injected subcutaneously (insert the needle at a 45-90° angle) using a 25-gauge needle into the upper arm, thigh or abdomen. • Doses greater than 4 ml should be injected into two separate sites. • Injection sites should be rotated. New injections should be given at least 2.5 cm from the previous site and never into areas where the site is tender, bruised, red, or hardened. **Administration: IV** • Infuse over 10 to 40 minutes; infusion must be completed within 1 hour of reconstitution. **N.B.** Refer to manufacturer PIL for specific considerations.
Emetogenicity	• IV, SC: Low (10% to 30%).
Warnings/ Precautions	**Hematological toxicities:** • Anemia, neutropenia, and thrombocytopenia are related to Azacitidine treatment, especially in the first two cycles. • Complete blood counts should be carried out to track toxicity and reaction, but at least before every cycle of therapy. Adjustments of subsequent doses may be needed. **Hepatic Toxicity:** • May be harmful to the liver in individuals who already have hepatic impairment. Patients with substantial tumor burden from metastatic disease, particularly those with baseline albumin <30 g/L, have been reported to experience progressive hepatic coma that ends in death. • Azacitidine is contraindicated in patients with advanced malignant hepatic tumors **Renal Toxicity:** • When IV Azacitidine is used in conjunction with other chemotherapy agents, kidney

	toxicities such as serum creatinine elevations, renal tubular acidosis (serum bicarbonate decrease to <20 mEq/L associated with alkaline urine and serum potassium <3 mEq/L), and kidney failure (some fatal) have been reported. • Renal toxicity may be more common in patients with impaired renal function. **Necrotizing Fasciitis:** • Post marketing reports of bacterial infection "necrotizing fasciitis", including fatal cases. Early symptoms include: a red, warm, or swollen area of skin that spreads quickly, severe pain in skin and area beyond, and fever. Later symptoms can include: ulcers, blisters, changes in the color of the skin. • If necrotizing fasciitis developed, stop Azacitidine therapy and start suitable treatment immediately. **Differentiation Syndrome:** • Patients using injectable Azacitidine have reported cases of differentiation syndrome, commonly referred to as retinoic acid syndrome. The signs and clinical findings of differentiation syndrome, which can be fatal, include fever, rash, pleural effusions, pericardial effusions, respiratory distress, pulmonary infiltrates, pulmonary edema, peripheral edema, rapid weight gain, hypotension, and renal failure. • The first indications of differentiation syndrome symptoms or signs should prompt consideration of treatment with high-dose intravenous corticosteroids and hemodynamic monitoring. • It is advisable to temporarily stop injectable Azacitidine until the symptoms have resolved. If resumed, exercise caution. **Cardiac and pulmonary disease:** • Patients with a known history of cardiovascular or pulmonary disease showed a significantly increased incidence of cardiac events with Azacitidine. Caution • A cardiopulmonary evaluation should be done both before and during treatment. **Injection-site reactions**: Injection site reactions commonly occurred with SC Azacitidine administration.
Storage and Light Sensitivity	• **Vial**: Store intact vials between 15°C to 30°C. • **After reconstitution:** Limited stability and must be prepared immediately before each dose. • **SC suspension**: Following reconstitution, suspension may be stored at room temperature for up to 1 hour prior to immediate administration (administer within 1 hour of reconstitution). The reconstituted product may be held under refrigerated conditions (2°C to 8°C) for up to 12 hours if water for injection used was at room temperature, or up to 30 hours if refrigerated water for injection is used. • After removal from refrigerator, reconstituted suspension may be held for up to 30 minutes prior to administration. **N.B.** Refer to manufacturer PIL for specific considerations.

Patient Counselling Keys	• This medicine lowers blood cell count. Avoid causes of infection and bleeding. Regular blood tests are required while receiving treatment. • This medication could be harmful to a fetus. Before you begin taking this medication, a pregnancy test will be performed to confirm that you are not pregnant. Use effective contraceptive during treatment. • If you have warm skin and rapidly spreading red or purple regions of swelling, or skin changes such as blisters, ulcers, or black areas call your doctor straight away. • Tell your physician if you experience any symptoms of liver disease, such as yellow skin or eyes, light-colored feces, light urine, fatigue, decreased appetite, and unsettled or painful stomach.
Sequence of Administration	• Cell cycle-specific with activity in the S phase.

2. Capecitabine

Generic Name	Capecitabine
Dosage Form/ Strengths	Tablets: 500 mg.
Route of Administration	Oral
Pharmacologic Category	Pyrimidine Analogue, Antimetabolite, Antineoplastic Agent ATC code: L01BC06
Indications	**N.B.** *Refer to literature and specific protocols for all indications*. • **Colon cancer**: Adjuvant therapy for patients with stage III. • **Metastatic Colorectal Cancer** • **Metastatic Breast Cancer:** In combination with docetaxel after failure of prior anthracycline-containing therapy. • **Metastatic Breast Cancer or Locally advanced**: As monotherapy after failure of Taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated. • **Advanced Gastric cancer**: First line in combination with a platinum-based regimen
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols.* • **Adults:** **Breast cancer and Monotherapy:** 1250 mg/m^2 twice daily for 2 weeks, followed by a 1-week rest period, given as 3-week cycles. Docetaxel dose 75 mg/m^2 1 hr. IV infusion on Day 1 of a 3-week cycle. **In combination with Colon, Colorectal, and Gastric cancer:** - 1250 mg/m^2 twice daily for 2 weeks, followed by a 1-week rest period. - Starting dose may be reduced to 800 – 1000 mg/m^2 twice daily for 2 weeks, followed by 1-week rest or to 625 mg/m^2 twice daily when administered continuously. Adjuvant treatment for colon cancer stage III needs a total of 8 cycles (24 weeks). • **Pediatrics:** Safety & efficacy not established.
Dosage Adjustment	**N.B.** *Refer to the protocol used for specific dose modifications*. • **Dosage in renal impairment:** **Note:** Capecitabine and its metabolites are primarily (>95%) excreted by the kidneys. - Mild renal dysfunction (CrCl 50-80 mL/min): No dose adjustments are required.

	- Moderate renal dysfunction (CrCl 30-50 mL/min): Reduce the starting dose to 75% of the 1250mg/m^2 dose. No dose reduction is required for a starting dose of 1000 mg/m^2. - Severe renal dysfunction (CrCl < 30 ml/min): Contraindicated, discontinue if impaired during treatment. • **Dosage in hepatic impairment:** Insufficient safety and efficacy data. Monitor and caution. • **Hepatotoxicity during treatment:** Hyperbilirubinemia of >3.0 x ULN or treatment related elevations in hepatic aminotransferases (ALT, AST) of >2.5 x ULN occur: Withhold Capecitabine and then resume when resolved at the same or at a reduced dose or permanently discontinue based on severity and occurrence. **Hematology**: If neutrophil count drops below 1.0 x 10^9 /L or that the platelet count drops below 75 x 10^9 /L, treatment with Capecitabine should be interrupted. **Other dose limiting toxicities:** include gastrointestinal toxicities and hand-foot syndrome. Most adverse reactions are reversible and do not require permanent discontinuation of therapy, although doses may need to be withheld or reduced.
Contra-indications	• Hypersensitivity to Capecitabine or Fluorouracil (5-FU). • Severe hepatic or renal impairment (CrCl <30 mL/min). • Complete or near complete absence of dihydropyrimidine dehydrogenase (DPD) activity. • Severe leucopenia, neutropenia, or thrombocytopenia (Do not treat patients with neutrophil <1.5 x 10^9/L or thrombocyte counts <100 x 10^9/L).
Adverse Drug Reactions	**Bone marrow depression** **Cardiotoxicity** **Dermatologic reactions (including hand-and-foot syndrome)** **GI toxicity** **>10%** **Cardiovascular**: Edema (≤15%) **Dermatologic**: Dermatitis (27% to 37%), palmar-plantar erythrodysesthesia (54% to 60%) **Gastrointestinal**: Abdominal pain (14% to 35%), anorexia (≤23%), constipation (≤15%), decreased appetite (26%), diarrhea (47% to 57%; grades 3/4: 2% to 13%), nausea (34% to 53%; grades 3/4: 2% to 4%), stomatitis (22% to 25%; grades 3/4: ≤7%), vomiting (15% to 37%; grades 3/4: ≤4%) **Hematologic & oncologic**: Anemia (72% to 80%, grades 3/4: ≤3%), lymphocytopenia (94%; grades 3/4: 15% to 44%), neutropenia (13% to 26%; grades 3/4: 1% to 3%), thrombocytopenia (24%; grades 3/4: 1% to 3%) **Hepatic**: Hyperbilirubinemia (22% to 48%)

	Nervous system: Asthenia (≤42%), fatigue (≤42%), pain (≤12%), paresthesia (21%; grade 3: 1%) **Ophthalmic**: Eye irritation (13% to 15%) **Respiratory**: Dyspnea (≤14%) **Miscellaneous**: Fever (≤18%) **1% to 10%** **Cardiovascular**: Atrial fibrillation, bradycardia, chest pain, hypertension, hypotension, myocarditis, pulmonary embolism, tachycardia, venous thrombosis **Dermatologic**: Alopecia, dermal ulcer, diaphoresis, erythema of skin, nail disease, pruritus, skin discoloration, skin photosensitivity, skin rash **Endocrine & metabolic**: Cachexia, decreased serum calcium (grades 3/4: 2%), dehydration, hot flash, hypertriglyceridemia, hypokalemia, hypomagnesemia, increased serum calcium (grades 3/4: 1%), increased thirst. **Gastrointestinal**: Abdominal distention, dysgeusia, dyspepsia, dysphagia, gastric ulcer, gastroenteritis, gastrointestinal hemorrhage, gastrointestinal inflammation (upper), gastrointestinal motility disorder (10%), intestinal obstruction, oral discomfort (10%), rectal pain, upper abdominal pain **Hematologic & oncologic**: Bone marrow depression, a disorder of hemostatic components of blood, granulocytopenia (grades 3/4: ≤2%), hemorrhage, leukopenia, lymphedema, pancytopenia **Hepatic**: Abnormal hepatic function tests, cholestatic hepatitis, hepatic fibrosis, hepatitis, increased serum alanine aminotransferase (grades 3/4: 2%) **Hypersensitivity**: Hypersensitivity reaction **Infection**: Fungal infection, sepsis, viral infection **Nervous system**: Ataxia, balance impairment, confusion, depression, dizziness, dysarthria, dysphasia, encephalopathy, headache, insomnia, lethargy (10%), mood changes, myasthenia, peripheral sensory neuropathy (10%), tremor, vertigo **Neuromuscular & skeletal**: Arthralgia, arthritis, back pain (10%), limb pain, myalgia **Ophthalmic**: Conjunctivitis, keratoconjunctivitis, visual disturbance **Renal**: Renal insufficiency **Respiratory**: Bronchitis, cough, epistaxis, flu-like symptoms, pharyngeal disease, pneumonia, respiratory distress **Miscellaneous**: Fibrosis, radiation recall phenomenon
Monitoring Parameters	• CBC with differential. • Liver function test (Bilirubin, AST, ALT). • Kidney function test baseline and periodically (High nephrotoxic effects). • Cardiac function (ECG) at baseline and during treatment. • Test for Dihydropyrimidine dehydrogenase DPD activity. • Monitor for serious skin reaction.

Drug Interactions	***Risk X: Avoid combination*** Abrocitinib, Allopurinol, Aminolevulinic Acid (Systemic), Baricitinib, BCG (Intravesical), BCG Products, Brivudine, Cedazuridine, Cladribine, Dengue Tetravalent Vaccine (Live), Deucravacitinib, Dipyrone, Etrasimod, Fexinidazole, Filgotinib, Gimeracil, Levoketoconazole, Mumps- Rubella- or Varicella-Containing Live Vaccines, Natalizumab, Pimecrolimus, Pimozide Poliovirus Vaccine (Live/Trivalent/Oral), Ritlecitinib, Ruxolitinib (Topical), Sertindole, Tacrolimus (Topical), Tofacitinib, Typhoid Vaccine, Upadacitinib Vaccines (Live), Yellow Fever Vaccine. ***Risk D: Consider therapy modification*** Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), Deferiprone, Denosumab, Domperidone, Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, QT-prolonging Agents (Highest Risk), Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T Vaccines (Inactivated/Non-Replicating), Vitamin K Antagonists (eg, warfarin).
Pregnancy and Lactation	**Pregnancy:** Avoid. May cause fetal harm when given to a pregnant woman. Capecitabine caused embryolethality and teratogenicity in animals. **Lactation**: Not recommended because significant amounts of Capecitabine metabolites have been found in breast milk in animal studies.
Administration	**Oral** • Administer with water within 30 minutes after a meal. • Administer doses at approximately the same times each day, nearly 12 hours apart. • Swallow tablets whole; do not cut, chew, or crush. If a dose is missed or vomited, continue with the next scheduled dose; do not administer an additional dose. **Hazardous agent** (NIOSH 2016 [group 1]): Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. **N.B.** Refer to manufacturer PIL for other specific considerations.
Emetogenicity	Minimal to low (<30%).
Warnings/ Precautions	• **Diarrhea** may be severe; interrupt capecitabine treatment immediately until diarrhea resolved; Administer fluid and electrolyte replacement and standard antidiarrheal treatments (e.g. Loperamide) if needed. • **Dehydration**: Prevent or correct at the onset. Dehydration may cause acute renal failure which may be fatal. Caution in patients with pre-existing renal impairment or concomitant nephrotoxic medicinal products. • **Cardiotoxicity:** including myocardial infarction, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, ECG changes, and

cardiomyopathy; more common with history of coronary artery disease. Symptoms often occur within 2-3 days after capecitabine is started. Discontinue treatment if occurs.

- **Severe skin reactions:** Capecitabine can induce severe skin reactions such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis. Capecitabine should be permanently discontinued in patients who experience a severe skin reaction during treatment**.**
- **Hand-foot skin syndrome:** also known as palmar-plantar erythrodysesthesia, refers to a condition where the palms of the hands and soles of the feet become dry, red, numb, and tingling, with or without associated swelling. Persistent or severe hand-foot syndrome (Grade 2 and above) can eventually lead to loss of fingerprints. If grade 2 or 3 hand- foot syndrome occurs, discontinue treatment until resolved or decrease in intensity to grade 1. Following grade 3 hand-foot syndrome, decrease subsequent doses of Capecitabine. Dexpanthenol may be used as prophylaxis in patients treated with Capecitabine.

- Grade 1: Numbness, tingling, painless swelling, or erythema of either hands or feet, or both including discomfort which does not disrupt the patient's normal activities.
- Grade 2 Painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities of daily living.
- Grade 3 hand-foot syndrome is moist desquamation, ulceration, blistering and severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living.

- **Hyperbilirubinemia:** Interrupt therapy immediately until it resolves or decreases in intensity. Treatment with Capecitabine may be resumed when bilirubin decreases to 3.0 x ULN or hepatic aminotransferases decreases to 2.5 x ULN. Monitor in mild to moderate hepatic impairment.
- **Hematology**: Bone marrow depression includes anemia, thrombocytopenia, and neutropenia. Do not treat patients with baseline neutrophil counts <1.5 x 10^9;/L or thrombocyte counts <100 x 10^9;/L; if grade 3-4 neutropenia or thrombocytopenia occurs, stop therapy until condition resolves.
- **Dihydropyrimidine dehydrogenase (DPD) deficiency:** Increased risk of severe or fatal adverse reactions in patients with low or absent dihydropyrimidine dehydrogenase (DPD) activity; withhold or permanently discontinue Capecitabine in patients with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity; no Capecitabine dose has been proven safe in patients with absent DPD activity.
  Patients can be tested for DPD deficiency by measuring the level of uracil (a substance broken down by DPD) in the blood, or by checking for the presence of certain mutations (changes) in the gene for DPD.
- **Elderly:** Patients ≥60 years of age may experience a greater incidence of

	treatment-related grade 3 or 4 adverse events (diarrhea, hand-and-foot syndrome, nausea/vomiting). • **Coumarin-derivative anticoagulation:** Monitor anticoagulant response closely (eg, INR, prothrombin time) and adjust anticoagulant dose accordingly. • **Caution** in patients with Diabetes mellitus, electrolyte disturbances, Hypo- or hypercalcemia: aggravation to symptoms may occur. • **Concurrent Proton pump inhibitors**: Concomitant use of proton pump inhibitors (PPIs) and Capecitabine may alter capecitabine dissolution and absorption due to higher gastric pH levels. • **Leucovorin or folic acid**: Adverse effects and toxicity of Fluorouracil Products may be enhanced by leucovorin, folic acid, or folate analog products.
Storage and Light Sensitivity	• Store between 15°C to 30°C. • Keep it in a tightly closed container. **N.B.** Refer to manufacturer PIL for other specific considerations.
Patient Counselling Keys	• This medicine may affect blood counts. Avoid causes of infection and bleeding. • Swallow tablets whole. If a dose is missed or vomited, continue with the next scheduled dose; do not administer an additional dose. • Tell your doctor if you are taking any drugs as you may need extra blood tests or your dose may need to be changed • Do not take products containing folic acid or folate analog products unless directed to do so by healthcare provider. • Call your doctor if any of these side effects or any other side effects: allergy reactions, signs of heart problems like chest pain; abnormal heartbeat; or shortness of breath, burning, numbness, or tingling feeling, redness or irritation of the palms of hands or soles of feet, diarrhea, dark urine, mouth irritation or mouth sores or change in eyesight, or Signs of bleeding.
Pharmaco-genomics	• **Dihydropyrimidine Dehydrogenase gene** Capecitabine is not recommended in DPD deficiency due to an increased risk for early-onset toxicity and serious, potentially fatal, adverse reactions, including mucositis, diarrhea, neutropenia, and neurotoxicity.

3. Cytarabine

Generic Name	Cytarabine
Dosage Form/ Strengths	• Solution for injection: 200mg/2ml, 100 mg/5ml, 500mg/5ml, 500 mg/10ml, 1000 mg/10ml, 1000 mg/20ml, 2000mg/20ml, 4000ml/80ml. • Lyophilized Powder: 100 mg/5ml
Route of Administration	Intravenous (injection or infusion), Intrathecal and Subcutaneous
Pharmacologic Category	Antineoplastic Agent, Antimetabolite (Pyrimidine Analog) ATC: L01BC01
Indications	**N.B.** Refer to literature and specific protocols for all indications used. **Acute lymphocytic leukemia** **Acute myeloid (non-lymphocytic) leukemia** of adults and pediatric patients. **Chronic myeloid leukemia:** in blast phase. **Meningeal leukemia:** Intrathecal administration of Cytarabine Injection (preservative free preparations only): Prophylaxis and treatment of meningeal leukemia. **Other indications:** Hodgkin (2nd line) and non- Hodgkin lymphoma.
Dosage Regimen	**N.B.** Different doses and regimens have been used; consult the literature for specific protocols. • **Intrathecally** - ***Range***: 5 mg/m^2 to 75 mg/m^2. - ***Frequency***: once a day for 4 days to once every 4 days. - ***Usual dose***: 30 mg/m^2 every 4 days until cerebrospinal fluid findings is normal, followed by one additional treatment. • **Intravenous** - ***Continuous treatment***: 2 mg/kg/day by rapid IV injection daily for ten days. Then may be increased to 4 mg/kg/day until a therapeutic response or toxicity is evident. **Or** start by 0.5 to 1 mg/kg/day in one-hour infusions, then increase to rate of 2 mg/kg/day until toxicity is observed. - ***Intermittent treatment***: 3-5 mg/kg daily, for five consecutive days, and can be repeated after rest period of 2 to 9 days, until the therapeutic response or toxicity is exhibited. - ***Another dosing***: Continuous infusion of 100-200 mg/m^2/24 hours for 5-7 days alone or combination with other cytostatics. Repeat at intervals of 2-4 weeks, until remission is achieved, or unacceptable toxicity occurs. - ***High dosage***: 2-3 g/m^2, as intravenous infusion, for 1-3 hours every 12 hours for 2-6 days (total of 12 doses per cycle). A total treatment should not exceed 36 g/m^2. Frequency of treatment cycles depends on response and toxicity.

	• **Maintenance therapy, Intravenous or subcutaneous:** To maintain remission, doses of 1 mg/kg may be given once or twice weekly. **Pediatric patients:** Tolerate higher doses than aadults
Dosage Adjustment	**N.B.** Refer to the protocol used for specific dose modifications. **Patients with Hepatic Impairment Dosing** Transaminases elevated (any elevation) or Bilirubin >2 mg/dL: Administer 50% of dose; may increase subsequent doses in the absence of toxicities. **Patients with Renal Impairment Dosing:** *CrCl 60 mL/minute or greater*: No dosage adjustment is needed. *CrCl 40 to 60 mL/minute:* ○ For doses more than 2 g/m^2 per dose, decrease the dose to 1 g/m^2 per dose. ○ For doses 750 mg to 1 g/m^2 per dose, decrease to 500 mg/m^2 per dose. *CrCl less than 40 mL/minute:* For doses more than 750 mg/m^2 per dose, give a dose less than or equal to 200 mg/m^2 per day. Cytarabine can be dialyzed. Therefore, Cytarabine should not be administered immediately before or after dialysis. **Elderly patients:** Caution. Monitor closely for toxicities.
Contra-indications	• Known hypersensitivity to Cytarabine or to any of the excipients. • Anemia, leucopenia, and thrombocytopenia of non-malignant etiology unless the benefits outweigh the risk. • Degenerative and toxic encephalopathies.
Adverse Drug Reactions	**Most Frequent Adverse Reactions:** Nausea, vomiting, anorexia, oral and anal inflammation or ulceration, rash, nausea, thrombophlebitis, vomiting, hepatic dysfunction, bleeding, diarrhea, fever.
Drug Interactions	***Risk X: Avoid combination*** Abrocitinib, Baricitinib, BCG (Intravesical), BCG Products, Brivudine, Cedazuridine, Cladribine, Dengue Tetravalent Vaccine (Live), Deucravacitinib, Fexinidazole, Filgotinib, Mumps- Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec Natalizumab, Pimecrolimus, Poliovirus Vaccine (Live/Trivalent/Oral), Ritlecitinib, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Typhoid Vaccine, Upadacitinib Vaccines (Live), Yellow Fever Vaccine. ***Risk D: Consider therapy modification*** Coccidioides immitis Skin Test COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), Deferiprone, Denosumab Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T Vaccines (Inactivated/Non-Replicating).

Monitoring Parameters	• CBC with differential and platelet count frequently. • Monitor for signs/symptoms of bleeding, infection, neutropenic fever. • Kidney and Liver function tests (periodic). • Serum uric acid (hyperuricemia). • Monitor pancreatic function (lipase and amylase)
Pregnancy and Lactation	**Pregnancy**: Avoid. Human Data is not sufficient. Potential fetal harm and teratogenicity particularly when administered in the first trimester. **Lactation**: Not recommended due to the potential serious adverse reactions in the breastfed infant.
Administration	**Administration: Intrathecal** Intrathecal doses should be administered as soon as possible after preparation. **Administration: IV** Infuse standard dose: 100 to 200 mg/m^2/day as a continuous infusion. High dose cytarabine has been infused over 1 to 3 hours according to protocols (refer to protocol) **Administration: Subcutaneous** May administer at concentration not to exceed 100 mg/mL: rotate injection sites. Antiemetics may be recommended to prevent nausea and vomiting before IV and Intrathecal. **Preparation for Administration (pediatrics and adults):** - Reconstitute powder with bacteriostatic water for injection. - For IV infusion: Further dilute in 250 to 1,000 mL of NS or D5W. - For subcutaneous: Dilute with bacteriostatic water for injection or NS to a concentration not to exceed 100 mg/mL. - Intrathecal: Reconstitute with preservative-free NS; may be further diluted to preferred final volume with preservative-free NS. After preparation, store intrathecal medications in an isolated location or container clearly marked with a label identifying as "intrathecal" use only. - Triple intrathecal therapy (TIT): Cytarabine with hydrocortisone sodium succinate and methotrexate are reported to be compatible together in a syringe with definite concentrations. Refer to literature. **Hazardous agent** (NIOSH 2016 [group 1]): Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. **N.B.** Refer to manufacturer PIL for specific considerations.
Emetogenicity	• Cytarabine >200 mg/m^2: Moderate emetic risk • Cytarabine (low dose) 100 mg/m^2– 200 mg/m^2: Low emetic risk • Cytarabine <100 mg/m^2: Minimal emetic risk
Warnings/ Precautions	• **A Cytarabine syndrome:** Characterized by fever, myalgia, bone pain, occasionally chest pain, maculopapular rash, conjunctivitis, and malaise. It

	usually occurs 6-12 hours following drug administration. Corticosteroids have been shown to be beneficial in treating or preventing this syndrome. **Eye disorders:** Reversible corneal lesion and haemorrhagic conjunctivitis occured. use prophylactic local corticosteroid eye drops. • **Bone marrow suppression:** The severity of these reactions are dose and schedule dependent. Therapy should be suspended or modified when platelet count reaches less than 50,000 or a polymorph nuclear count below 1000 per mm^3. Following 5-day injections of 50 mg/m^2 to 600 mg/m^2, white cell depression follows a biphasic course. There is an initial fall starting the first 24 hours with a nadir at days 7-9 followed by a brief rise. A second and deeper fall reaches nadir at days 15-24. Then there is rapid rise to above baseline in the next 10 days. • **CNS, GI and pulmonary toxicity (Severe, sometimes fata):** Cerebral and cerebellar dysfunction, including personality changes, somnolence and coma, usually reversible. Severe hepatobiliary and gastrointestinal disorders: ulceration; sepsis and liver abscess; liver damage; bowel necrosis; and necrotizing colitis. Pulmonary toxicities: Potentially fatal syndrome of sudden respiratory distress (SRD) reported following after experimental high dose therapy including cough, dyspnea, fever, tachypnea, hypoxemia, pneumonia, and interstitial and alveolar infiltrates progressing to pulmonary edema and cardiomyopathy. Pulmonary edema typically occurs 1-2 weeks after therapy, often after the first course. • **Pancreatitis**: There have been reports of acute pancreatitis in patients receiving continuous infusion cytarabine and in patients receiving cytarabine who were previously treated with L-asparaginase. • **High dosing** of Cytarabine should be observed for neuropathy since dose adjustments may be needed to avoid irreversible neurologic disorders. • **Delayed progressive paralysis** resulting in death has been reported in children with AML following intrathecal and intravenous cytarabine at conventional doses in combination with other drugs. • **Benzyl alcohol**: Some products may contain benzyl alcohol. Benzyl alcohol is associated with gasping syndrome in premature infants. Not for intrathecally or high-dose cytarabine regimens.
Storage and Light Sensitivity	• Store intact vials at 15°C to 30°C. Do not refrigerate or freeze. • Protect from light. **N.B.** Refer to manufacturer PIL for specific considerations.
Patient Counseling Points	• This drug induces low blood cell counts. Avoid infections and bleeding causes. • A blood test may be taken before each treatment. The dose and timing of your chemotherapy may be changed based on test results and/or other side effects. • Call doctor if any of these signs appeared (e.g. bleeding, infection, upset stomach, stomach pain, throwing up, diarrhea, decreased appetite, yellow skin

	or eyes, dark or bloody urine, unable to pass urine, very bad back pain, numbness or tingling in the hands or feet, stiff neck, very bad muscle weakness, shortness of breath, chest pain, change in eyesight, eye pain, or severe eye irritation.) • This drug is teratogenic. You should not become pregnant while using cytarabine.
Sequence of Administration	• Cell cycle specific (S phase). • When combined with Fludarabine, Cytarabine shuld be given second for enhanced efficacy.

4. Fluorouracil

Generic Name	Fluorouracil
Dosage Form/ Strengths	• Concentrate for solution for injection/infusion: 250 mg/5ml, 500 mg/10ml, 1000 mg/20ml. • Tablets: 50 mg. • Topical Cream: 50 mg/gm.
Route of Administration	IV, Topical, Oral
Pharmacologic Category	Antimetabolite antineoplastic agent acts as a pyrimidine antagonist. ATC: L01BC02
Indications	**N.B.** *Refer to literature and specific protocols for all indications***.** **Systemic** Colorectal cancer. Breast cancer. Gastric (stomach) cancer. Pancreatic cancer. **Other uses** Head and neck, esophageal and Bladder cancer. **Topical** Actinic keratosis. Basal cell carcinoma.
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols***.** **Recommended adult dosing:** **Adenocarcinoma of the Colon and Rectum (**in combination with leucovorin and oxaliplatin or irinotecan, or with leucovorin alone**):** **IV**: 400 mg/m^2 by intravenous bolus on Day 1, followed by 2400 mg/m^2 to 3000 mg/m^2 as a continuous infusion over 46 hours every two weeks. **Adenocarcinoma of the Breast** (as a component of a cyclophosphamide-based multidrug regimen) **IV**: 500 mg/m^2 or 600 mg/m^2 on Days 1 and 8 every 28 days for 6 cycles. **Gastric Adenocarcinoma** (as a component of a platinum-containing multidrug regimen): **IV**: 200 mg/m^2 to 1000 mg/m^2 as a continuous infusion over 24 hours. **Pancreatic Adenocarcinoma:** **IV**: 400 mg/m^2 intravenous bolus on Day 1, followed by 2400 mg/m^2 as a continuous infusion over 46 hours every two weeks. **Other recommended dosing (as single agent)** **Inintial: IV infusion:** 15mg/kg (do not exceed 1g per infusion) over 4 hours (alternatively over 30 - 60 minutes or over 24 hours). The infusion may be

	repeated daily until there is evidence of toxicity or a total dose of 12 - 15g has been reached. **Maintainance** Then dose can be repeated after an interval of 4 to 6 weeks. **Or IV:** 15mg/kg once a week kg (do not exceed 1g per infusion) to obviate the need for an initial period of daily administration. **Pediatric Use:** The safety and effectiveness in pediatric patients have not been established. **Topical**: Apply twice daily for 2-4 weeks
Dosage Adjustment	**N.B.** *Refer to protocol used for specific dose modifications*. **Obesity**: Dosing in adults with a BMI ≥30 kg/m^2: the ideal weight or estimated lean body mass should be used. **Dosing: Altered Kidney Function: Adult** There are no dosage adjustments necessary. Consider 30- 50% dose reduction for starting doses. **Dosing: Hepatic Impairment: Adult** Mild or moderate impairment (without concomitant renal impairment): Consider 30- 50% dose reduction for starting doses. Severe impairment: Use is not recommended; avoid use. **The initial dose should be reduced by 30-50% in patients with any of the following**: • Cachexia. • Major surgery within preceding 30 days • Reduced bone marrow function: If Leukocytes 2.5 - 3.5 10^9 /l or Thrombocytes 75 – 125 10^9 /l: use 50% of the recommended dose. Suspend if less than that. **Dosing: Adjustment for Toxicity: Adult** Withhold treatment for the following (may resume at a reduced dose following resolution or improvement to grade 1): • Dermatologic toxicity: Grade 2 or 3 palmar-plantar erythrodysesthesia (hand-foot syndrome [HFS]); initiate supportive care for symptomatic relief of HFS. • GI toxicity: Grade 3 or 4 diarrhea (administer fluids, electrolyte replacement, and/or antidiarrheal treatments as necessary); grade 3 or 4 mucositis. • Hematologic toxicity: Grade 4 myelosuppression. Withhold treatment for the following (there is no recommended dose for resumption): • Cardiovascular toxicity: Angina, MI/ischemia, arrhythmia, or heart failure (in patients with no history of coronary artery disease or myocardial dysfunction) • CNS toxicity: Acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbances • Hyperammonemic encephalopathy (initiate ammonia-lowering therapy).

	Evidence of acute early-onset or unusually severe toxicity indicative of dihydropyrimidine dehydrogenase (DPD) deficiency: Withhold or permanently discontinue fluorouracil depending on the onset, duration, and severity of toxicity.
Contra-indications	• Hypersensitivity • Bone marrow suppression • Dihydropyrimidine dehydrogenase (DPD) deficiency • Infection • Malnutrition • Pregnancy
Adverse Drug Reactions	**Cardiotoxicity** **GI toxicity** **Palmar-plantar erythrodysesthesia** **Bone marrow suppression** **Hyperammonemic encephalopathy** **Adverse events:** **Cardiovascular**: Angina pectoris, cardiac arrhythmia, cardiac failure, cerebrovascular accident, ischemic heart disease, local thrombophlebitis, myocardial infarction, vasospasm, ventricular ectopy **Central nervous system**: Cerebellar syndrome (acute), confusion, disorientation, euphoria, headache **Dermatologic**: Alopecia, changes in nails (including nail loss), dermatitis, hyperpigmentation (supravenous), maculopapular rash (pruritic), palmar-plantar erythrodysesthesia, skin fissure, skin photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, xeroderma **Gastrointestinal**: Anorexia, diarrhea, esophagopharyngitis, gastrointestinal hemorrhage, gastrointestinal ulcer, mesenteric ischemia (acute), nausea, stomatitis, tissue sloughing (gastrointestinal), vomiting **Hematologic & oncologic**: Agranulocytosis, anemia, leukopenia (nadir: days 9 to 14; recovery by day 30), pancytopenia, thrombocytopenia **Hypersensitivity**: Anaphylaxis, hypersensitivity reaction (generalized) **Ophthalmic**: Lacrimal stenosis, lacrimation, nystagmus, photophobia, visual disturbance **Respiratory**: Epistaxis
Monitoring Parameters	• CBC with differential. • Baseline evaluation of cardiac functions (by history, physical examination, ejection fraction and ECG) • Liver and kidney function test. • INR, and prothrombin time (monitor closely in patients receiving concomitant coumarin-derivative anticoagulants). • Test for dihydropyrimidine dehydrogenase DPD activity. • Monitor for adverse effects.
Drug Interactions	***Risk X: Avoid combination***

	Abrocitinib, Allopurinol, Aminolevulinic Acid (Systemic), Baricitinib, BCG (Intravesical), BCG Products, Brivudine, Chloramphenicol (Systemic), Cladribine, Dengue Tetravalent Vaccine (Live), Deucravacitinib, Dipyrone, Etrasimod, Fexinidazole, Filgotinib, Gimeracil, Levoketoconazole, Mumps- Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Pimozide, Poliovirus Vaccine (Live/Trivalent/Oral), Ritlecitinib, Ruxolitinib (Topical), Sertindole, Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Typhoid Vaccine, Upadacitinib, Vaccines (Live), Yellow Fever Vaccine. ***Risk D: Consider therapy modification*** Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), Deferiprone, Denosumab, Domperidone, Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, QT-prolonging Agents (Highest Risk), Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating), Vitamin K Antagonists (eg, warfarin).
Pregnancy and Lactation	**Pregnancy**: There is positive evidence of human fetal risk. Patients should use an effective contraception during treatment with fluorouracil and up to 6 months afterwards. Possibile irreversible infertility for men after treatment with Fluorouracil. **Breastfeeding**: Not recommended due to the potential secretion into breast milk and potential harm to infant.
Administration	**Hazardous agent** (NIOSH 2016 [group 1]): Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. **Administration: IV** • IV administration rate varies by protocol; refer to specific reference for protocol. • May be administered by IV push, IV bolus, or as a continuous infusion. • Fluorouracil may be an irritant; avoid extravasation. **IV infusion**: Further dilute in NS or D_5W for infusion. • **Intermittent infusion:** Dilute in 50 mL- 500ml given over 15min. to 4 hours. • **Continuous infusion**: over 24 hours or greater; may be given via an ambulatory infusion device. **IV push**: May dispense undiluted in a syringe over 2-4 minute. • When administering bolus Fluorouracil, 30 minutes of cryotherapy is recommended to prevent oral mucositis. **N.B**. Refer to manufacturer PIL for specific considerations.
Emetogenicity	Emetogenic potential: rare (< 10%)
Warnings/ Precautions	• **Cardiotoxicity**: Fluorouracil may cause cardiotoxicity (angina, MI/ischemia, arrhythmia, and heart failure). Interruption of treatment is recommended. Risk factors for cardiotoxicity include continuous infusion administration (versus IV

bolus) and coronary artery disease and the use of concurrent radiation or anthracyclines. Most cases of Fluorouracil-induced cardiotoxicities resolve after termination of Fluorouracil infusion and/or administration of nitrates or calcium channel blockers.

Fluorouracil has the second highest incidence of chemotherapy induced cardiotoxicity, after the anthracyclines. The incidence of fluorouracil induced cardiotoxicity can be as high as 8%. (magnitude: moderate/major).

- **GI toxicity**: Fluorouracil is associated with severe diarrhea. Mucositis, stomatitis, or esophagopharyngitis (which may lead to mucosal sloughing or ulceration) may occur with fluorouracil. The incidence of mucositis is reported to be higher with IV bolus fluorouracil administration (vs continuous infusion).
- **Palmar-plantar erythrodysesthesia: (**PPE), also called hand-foot skin reaction, may occur in association with the continuous infusion of fluorouracil. Symptoms of HFS include a tingling sensation, pain, swelling, erythema with tenderness, and desquamation. PPE may gradually disappear over 5-7 days after discontinuance of fluorouracil therapy. The onset of HFS is usually after 8 to 9 weeks of fluorouracil, although may occur earlier.
- **Bone marrow suppression**: Fluorouracil can cause severe and fatal hematologic toxicity (neutropenia, thrombocytopenia, and anemia). The neutrophil nadir usually occurs between 9 to 14 days after administration.
- **Hyperammonemic encephalopathy**: Fluorouracil may rarely result in hyperammonemic encephalopathy (altered mental status, coma, or ataxia, with high serum ammonia level). Onset was within 72 hours after fluorouracil infusion initiation. Resuming fluorouracil after case resolved has not been studied.
- Increase dietary intake of thiamine.
- If intractable vomiting occurs, fluorouracil should be immediately discontinued.
- **Leucovorin calcium** enhance the efficacy of fluorouracil, so combined therapy of fluorouracil and leucovorin should be used with caution in geriatric or debilitated patients as toxicity is increased.
- **Neurotoxicity**: Fluorouracil may cause neurologic toxicity, including acute cerebellar syndrome and other neurologic events (postmarketing reports). Neurologic symptoms included confusion, disorientation, ataxia, or visual disturbances. There are insufficient data on the risks of resuming fluorouracil in patients with resolved neurologic toxicity.
- **Dihydropyrimidine dehydrogenase deficiency**: Patients with partial DPD activity may be at increased risk for acute early onset of toxicity and severe, or fatal adverse reactions. Withhold or permanently discontinue fluorouracil in patients with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity. There is no Fluorouracil dose that has been proven safe in patients with complete absence of DPD activity and data are insufficient to recommend a specific dose in patients with partial DPD activity as measured by any specific test.

	• **Anticoagulant dose** may need adjustment. Closely monitor INR and prothrombin time in patients receiving fluorouracil and coumarin-derivative anticoagulants such as warfarin.
Storage and Light Sensitivity	• Store intact vials between 20°C to 25°C. Do not freeze. Protect from light. • Fluorouracil in use may be stored for 5 days at 20°C to 25°C. • Protect from light for (IV and topical) **N.B**. Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• This drug lowers blood cell counts. Avoid infections and bleeding causes. • Cardiotoxicity may occur. Contact healthcare provider immediately if new onset of chest pain, shortness of breath, dizziness, or lightheadedness. • Neurotoxicity may occur. Immediately contact a healthcare provider for new onset of confusion, disorientation; difficulty with balance or coordination; or visual disturbances • Tell healthcare provide about all drugs they are taking, including warfarin or other coumarin-derivative anticoagulants. • Contact their healthcare provider for severe diarrhea or for painful mouth sores with decreased oral intake of food or fluids. • This drug is Teratogenic. Use effective contraception during treatment with Fluorouracil and for up to 3 months after the last dose of Fluorouracil.
Sequence of Administration	• Cell-cycle specific. • Irritant and may cause chemical phlebitis. • When combined with methotrexate, Fluorouracil should be given first for better response and survival rate. • When combined with irinotecan, Fluorouracil should be given second for additive efficacy and less toxicity. • When combined with gemcitabine, docetaxel, oxaliplatin, or paclitaxel, Fluorouracil may be given second. • When combined with cisplatin or carboplatin, Fluorouracil may be given first for less toxicity.
Pharmaco-genomics	**Dihydropyrimidine dehydrogenase (DPD)** • Dihydropyrimidine dehydrogenase (DPD) is responsible for the metabolism of fluoropyrimidines (Fluorouracil, Capecitabine). Deficiency or low levels of this enzyme lead to elevated concentrations of 5-FU and higher risk for acute early-onset of toxicity and severe or fatal adverse reactions. • Phenotype and/or genotype testing is therefore recommended before starting treatment with Fluorouracil. • Patient who completely lacks DPD must not be given any systemic Fluorouracil medicines. For patients with partial deficiency, the doctor may consider starting cancer treatment at lower doses than normal or stopping treatment if severe side effects occur.

- Patients can be tested for DPD deficiency by measuring the level of uracil (a substance broken down by DPD) in the blood, or by checking for the presence of certain mutations (changes) in the gene for DPD.

5. Gemcitabine

Generic Name	Gemcitabine
Dosage Forms/ Strengths	**Powder for Solution for I.V Infusion:** 1 gm, 200 mg **Concentrate for Solution For I.V Infusion:** 200 mg/5ml, 1000 mg/100ml, 1000mg/26.316ml, 2000 mg/50 ml.
Route of Administration	IV
Pharmacologic Category	Antineoplastic Agent, Antimetabolite (Pyrimidine Analog). ATC Code: L01BC05.
Indications	**N.B.** Refer to literature and specific protocols for all indications**.** • **Bladder cancer,** locally advanced or metastatic, in combination with Cisplatin**.** • **Pancreatic Cancer: L**ocally advanced or metastatic adenocarcinoma of the pancreas. • **Non-small cell lung cancer:** locally advanced, or metastatic, as first-line treatment (in combination with cisplatin). • **Ovarian cancer:** locally advanced or metastatic**,** in combination with Carboplatin, in patients with relapsed disease following a recurrence-free interval of at least 6 months after platinum-based, first-line therapy. • **Breast cancer:** Unresectable, locally recurrent, or metastatic breast cancer in combination with paclitaxel, following adjuvant/neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline unless clinically contraindicated.
Dosage Regimen	**N.B.** Different doses and regimens have been used; consult the literature for specific protocols **Adult Dosing:** • **Breast cancer:** ○ 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. Given after IV Paclitaxel (175 mg/m^2) infusion over 3 hours on day 1, • **Non-small Cell Lung Cancer (NSCLC):** ○ Every 4-week schedule: 1000 mg/m^2 over 30 minutes on Days 1, 8, and 15 of each 28-day cycle ○ Every 3-week schedule: 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. Either schedule is followed by Cisplatin 100 mg/m^2 on Day 1. • **Ovarian cancer, advanced**: ○ 1000 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. Followed by Carboplatin given on day 1, consistent with a target Area Under Curve (AUC) of 4 mg/ml/min. • **Pancreatic Cancer:** ○ 1000 mg/m^2 over 30 minutes once weekly for the first 7 weeks, then one-week rest, then once weekly for 3 weeks of each 28-day cycle.

	Pediatric population: Gemcitabine is not recommended for use in children under 18 years of age due to insufficient data on safety and efficacy.
Dosage Adjustment	**N.B.** Refer to protocol used for specific dose modifications. • **Altered Kidney Function:** No dosing recommendation due to insufficient information. Caution should be used in patients with renal dysfunction. • **Hepatic Impairment:** No dosing recommendation due to insufficient information. Caution should be used in patients with hepatic dysfunction. • **Hematological toxicities:** If ANC 500-1000 10^6 /L or platelets 50,000-100,000 (x106 /l): Administer 75% of the full dose. If ANC < 500 10^6 /L or platelets < 50,000 (x106 /l): Hold • **Non-hematological toxicities:** **Permanently discontinue** in any of the following: severe pulmonary toxicity, Severe hepatic toxicity, Hemolytic-uremic syndrome, Capillary leak syndrome, Posterior reversible encephalopathy syndrome.
Contra-indications	• Known hypersensitivity to gemcitabine or any component of the formulation.
Adverse Drug Reactions	**Hypersensitivity** **Myelosuppression** **Hepatic Toxicity** **Pulmonary Toxicity and Respiratory Failure** **Hemolytic Uremic Syndrome** **>10%** **Cardiovascular**: Peripheral edema (20%), edema (≤13%) **Central nervous system**: Drowsiness (11%) **Dermatologic**: Skin rash (30%), alopecia (15%) Gastrointestinal: Nausea and vomiting (69%), diarrhea (19%), stomatitis (11%; grade 3: <1%) **Genitourinary**: Proteinuria (45%), hematuria (35%) **Hematologic & oncologic**: Anemia (68%; grade 3: 7%; grade 4: 1%), neutropenia (63%; grade 3: 19%; grade 4: 6%), thrombocytopenia (24%; grade 3: 4%; grade 4: 1%), hemorrhage (17%; grade 3: <1%; grade 4: <1%) **Hepatic**: Increased serum alanine aminotransferase (68%), increased serum aspartate aminotransferase (67%), increased serum alkaline phosphatase (55%), hyperbilirubinemia (13%) **Infection**: Infection (16%) **Renal**: Increased blood urea nitrogen (16%) **Respiratory**: Dyspnea (23%), flu-like symptoms (19%) **Miscellaneous**: Fever (41%) **1% to 10%**

	Central nervous system: Paresthesia (10%) **Local**: Injection site reaction (4%) **Renal**: Increased serum creatinine (8%) **Respiratory**: Bronchospasm (<2%) **Frequency not defined** Hypersensitivity: Nonimmune anaphylaxis.
Monitoring Parameters	• CBC with differential (frequently). • Liver function test. • Renal function test. • Monitor for toxicities. • Evaluate pregnancy status prior to treatment initiation.
Drug Interactions	***Risk X: Avoid combination*** Abrocitinibm, Baricitinib, BCG (Intravesical), Brivudine, Cedazuridine, Cladribine, Dengue Tetravalent Vaccine (Live), Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Mumps- Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Poliovirus Vaccine (Live/Trivalent/Oral), Ritlecitinib, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tofacitinib, Typhoid Vaccine, Upadacitinib, Vaccines (Live), Yellow Fever Vaccine. ***Risk D: Consider therapy modification*** Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), Deferiprone, Denosumab, Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-TVaccines (Inactivated/Non-Replicating).
Pregnancy and Lactation	**Pregnancy:** Gemcitabine may cause fetal harm if administered during pregnancy based on animal studies. Advise patients of reproductive potential to use effective contraception during treatment and for 6 months after the last dose for females and males. Possible infertility for men after treatment with Gemcitabine. **Lactation**: Avoid due to the potential serious adverse reactions in nursing infants.
Administration	**Administration: IV** • Infuse over 30 minutes. • This medicinal product may be reconstituted with sodium-containing solutions. • May be irritant and may cause chemical phlebitis. **Preparation of administration:** • Lyophilized powder: Reconstitute lyophilized powder with preservative free sodium chloride; add 5 mL to the 200 mg vial, add 25 mL to the 1,000 mg vial, or add 50 mL to the 2,000 mg vial, resulting in a reconstituted concentration of 38 mg/mL. Concentrations greater than 38 mg/ml may result in incomplete dissolution.

	• Concentrates may be further diluted with sodium chloride (0.9%) solution for injection. • Inspect the solution visually. If particulate matter or discoloration is found, do not administer. **If extravasation occurs,** Infusion must be stopped immediately and started again in another blood vessel. The patient should be monitored carefully after the administration. Nonvesicants but may cause chemical phlebitis. **Hazardous agent (NIOSH 2016 [group 1]):** Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. **N.B.** Refer to manufacturer PIL for specific considerations.
Emetogenicity	Low (10% to 30%).
Storage and Light sensitivity	• **Intact vials:** Store between 15°C to 30°C. • **Reconstituted solution:** Chemical and physical stability has been demonstrated for 35 days at 25°C. • **Diluted Solutions:** for infusion in neutral saline are stable for 24 hours at room temperature. Do not refrigerate (may result in crystallization). **N.B.** Refer to manufacturer PIL for specific considerations.
Warnings/ Precautions	**Schedule-Dependent Toxicity:** Prolongation of the infusion time beyond 60 minutes or more frequent than weekly dosing resulted in an increased incidence of clinically significant hypotension, severe flu-like symptoms, myelosuppression, and asthenia. **Myelosuppression:** • Myelosuppression manifested by neutropenia, thrombocytopenia, and anemia occurs with Gemcitabine as a single agent and the risks are increased when Gemcitabine is combined with other cytotoxic drugs. • Monitor patients receiving Gemcitabine Injection prior to each dose with a complete blood count (CBC), including differential and platelet count. **Pulmonary Toxicity and Respiratory Failure:** • Pulmonary toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome (ARDS), which may be fatal despite discontinuation of therapy. The onset may occur up to 2 weeks after the last dose of Gemcitabine. • Permanently discontinue Gemcitabine Injection in patients who develop unexplained dyspnea, with or without bronchospasm, or have any evidence of pulmonary toxicity. **Hemolytic Uremic Syndrome:** • Hemolytic uremic syndrome (HUS), including fatalities from renal failure or the requirement for dialysis, can occur in patients treated with Gemcitabine. • Assess renal function prior to initiation of Gemcitabine Injection and

periodically during treatment.

- Permanently discontinue Gemcitabine Injection in patients with HUS or severe renal impairment. Renal failure may persist even with discontinuation of therapy.

Hepatic Toxicity:

- Drug-induced hepatic injury, including hepatic failure and death, has been reported in patients receiving Gemcitabine alone or in combination with other potentially hepatotoxic drugs. Permanently discontinue gemcitabine in patients that develop severe hepatotoxicity.
- Administration of Gemcitabine in patients with concurrent hepatic metastases or a pre-existing hepatic disease can lead to exacerbation of the underlying hepatic insufficiency.
- Assess hepatic function prior to initiation of Gemcitabine Injection and periodically during treatment.

Exacerbation of Radiation Therapy Toxicity:

- Gemcitabine is not recommended for use in combination with radiation therapy.
- Concurrent (given together or less or equal than 7 days apart) — Life-threatening mucositis, especially esophagitis and pneumonitis occurred.
- Non-concurrent (given more than 7 days apart) — Excessive toxicity has not been observed when gemcitabine is administered more than 7 days before or after radiation.

Capillary Leak Syndrome:

- Capillary leak syndrome (CLS) with severe consequences has been reported in patients receiving gemcitabine as a single agent or in combination with other chemotherapeutic agents. Permanently discontinue Gemcitabine Injection if CLS develops during therapy.
- The clinical features include generalized edema, weight gain, hypoalbuminemia, severe hypotension, acute renal impairment and pulmonary edema. Usually treatable if recognized early and managed appropriately.

Posterior Reversible Encephalopathy Syndrome:

- Symptoms include hypertension, seizure, headache, lethargy, confusion, blindness, and other visual and neurologic disturbances.
- Confirm the diagnosis of PRES with magnetic resonance imaging (MRI) and permanently discontinue Gemcitabine Injection and implement supportive measures, including blood pressure control and anti-seizure therapy if PRES develops during therapy.

Patient Counselling Keys	• This drug induces low blood cell counts. Avoid infections and bleeding causes. • Call doctor if you have any of these symptoms: signs of bleeding, infection, hypertension, seizure, muscle pain, cramps, signs of CLS like edema, weight gain, urination disorders; a fast or abnormal heartbeat or chest pain. • Talk with your doctor before getting any vaccines.

	• Lung, Liver or kidney problems have happened with this drug. Call your doctor right away if you have shortness of breath or other trouble breathing.
Sequence of Administration	• Cell cycle-specific for the S-phase of the cycle. Also blocks cellular progression at G1/S-phase. • Nonvesicants may cause chemical phlebitis. • When combined with Cisplatin or other platinum agents, Gemcitabine should be given first for less toxicity. • When combined with Paclitaxel, Gemcitabine should be given second for less hepatotoxicity risk. • When combined with Pemetrexed, Gemcitabine should be given second for less toxicity and more efficaceous.

ANTIMICROTUBULE AGENTS

A. Taxanes

1. Docetaxel

Generic Name	Docetaxel
Dosage Form/ Strengths	Concentrate for Solution For I.V Infusion: 10mg, 20mg, 80mg, 140mg, 160mg.
Route of Administration	IV
Pharmacologic Category	Antineoplastic Agent, Antimicrotubular, Taxane Derivative ATC code: L01CD01
Indications	***N.B.*** *Refer to literature and specific protocols for all indications used* • Breast cancer • Non-small cell lung cancer • Prostate cancer (castration-resistant) • Gastric adenocarcinoma • Head and neck cancer **Other indications** Anal carcinoma, bladder cancer, Esophageal cancer, ewing sarcoma, osteosarcoma, ovarian cancer, small cell lung cance, soft tissue sarcoma, thyroid carcinoma, uterine neoplasms.
Dosage Regimen	***N.B****. Different doses and regimens have been used; consult the literature for specific protocols.* **Premedications are recommended** to reduce the incidence and severity of hypersensitivity reactions and fluid retention**.** **Recommended Adult Dosing**: Docetaxel is administered as a one-hour infusion every three weeks. **Locally advanced or metastatic breast cancer (monotherapy or in combination)**: 60mg/m^2 to 100 mg/m^2. **Breast cancer as adjuvant**: 75mg/m^2 administered 1 hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 cycles. **Non-small cell lung cancer**: - NSCLC: after platinum therapy failure: 75 mg/m^2 Single Agent - NSCLC: chemotherapy naive: 75 mg/m^2 followed by cisplatin 75 mg/m^2 **Prostate cancer**: 75 mg/m^2. Prednisone or prednisolone 5 mg orally twice daily is administered continuously. **Gastric adenocarcinoma:** 75 mg/m^2 followed by cisplatin 75 mg/m^2 (both on day 1 only) followed by fluorouracil 750 mg/m^2 per day as a 24-hour IV (days 1–5), starting at end of cisplatin infusion. **Head and neck cancer:** - 75 mg/m^2 followed by cisplatin 75 mg/m^2 IV (day 1), followed by fluorouracil 750 mg/m^2 per day as a 24-hr IV (days 1–5), starting at end of cisplatin infusion; for 4 cycles.

	- 75 mg/m^2 followed by cisplatin 100 mg/m^2 IV (day 1), followed by fluorouracil 1000 mg/m^2 per day as a 24-hr IV (days 1–4); for 3 cycles. **Pediatrics**: The safety and efficacy of Docetaxel have not been established**.**
Dosage Adjustment	***N.B.*** *Refer to protocol used for specific dose modifications.* **Dosing: Altered Kidney Function: Adult** No dosage adjustment is necessary. **Dosing: Hepatic Impairment: Adult** • AST/ALT >1.5 times ULN and alkaline phosphatase ≥2.5 times ULN: Avoid. May administer dose 75mg/m^2 (in case original dose is 100mg/m^2). Higher risk of developing severe adverse reactions. **N.B.** In combination with cisplatin and 5-fluorouracil use is not recommended. • AST/ALT >3.5 times ULN and alkaline phosphatase ≥6 times ULN: Docetaxel should not be used. **Dosing: Adjustment for Toxicity: Adult:** - Hematologic toxicity (includes febrile neutropenia, neutrophils <500/mm^3 for >1 week, severe or cumulative cutaneous reactions): Dose of docetaxel should be reduced from 100 mg/m^2 to 75 mg/m^2 and/or from 75 to 60 mg/m^2. - Dermatologic toxicity: Consider permanent docetaxel discontinuation in severe cutaneous adverse reactions. - Hypersensitivity: Immediately discontinue docetaxel for severe hypersensitivity reaction (and administer appropriate medical management). Do not rechallenge. - Neurosensory symptoms (eg, paresthesia, dysesthesia, pain): Adjust docetaxel dose for severe neurosensory symptoms; discontinue Docetaxel for persistent symptoms. - Ocular disorders: Discontinue Docetaxel if cystoid macular edema is diagnosed (consider alternate non-taxane therapies). A prompt comprehensive ophthalmic exam is recommended if vision impairment occurs.
Contra-indications	• Hypersensitivity to the active substance or any of the excipients. • Baseline neutrophil count of < 1,500 cells/mm^3. • Pregnant or breast-feeding. • Severe liver impairment (no data available).
Adverse Drug Reactions	**>10%** **Dermatologic**: Alopecia (56% to 76%, can be permanent), dermatological reaction (20% to 48%; severe dermatological reaction: 5%), nail disease (11% to 41%). **Endocrine & metabolic**: Fluid retention (26% to 60%). **Gastrointestinal**: Diarrhea (23% to 43%; severe diarrhea: ≤6%), nausea (34% to

	42%; severe nausea: ≤5%), stomatitis (19% to 53%; grades 3/4: 2%), vomiting (22% to 23%; severe vomiting: ≤5%). **Hematologic & oncologic**: Anemia (65% to 97%; grades 3/4: 8% to 9%), febrile neutropenia (5% to 14%), leukopenia (84% to 99%; grades 3/4: 49%; grade 4: 32% to 44%), neutropenia (84% to 99%; grades 3/4: 65%; grade 4: 75% to 86%; nadir [median]: 7 days, duration [severe neutropenia]: 7 days), thrombocytopenia (7% to 14%; grades 3/4: 3%; grade 4: 1%). **Hepatic**: Increased serum alanine aminotransferase (≤19%), increased aspartate aminotransferase (≤19%). **Hypersensitivity**: Hypersensitivity reaction (6% to 21%, including back pain, chest tightness, chills, drug fever, dyspnea, flushing, skin rash; severe hypersensitivity reaction: 3% to 4%). **Infection**: Infection (1% to 34%; severe infection: 2% to 6%). **Nervous system**: Central nervous system toxicity (20% to 58%; including dysesthesia: ≤6%, paresthesia: ≤6%). **Neuromuscular & skeletal**: Asthenia (53% to 66%; severe weakness: 13% to 18%), myalgia (3% to 23%; severe myalgia: 2%), neuromuscular reaction (16%). **Respiratory**: Pulmonary disease (41%). **Miscellaneous**: Fever (31% to 35%). **1% to 10%** **Cardiovascular**: Hypotension (3%). **Gastrointestinal**: Dysgeusia (6%). **Hepatic**: Increased serum alkaline phosphatase (7%), increased serum bilirubin (9%). **Local**: Infusion site reaction (4%; including erythema at injection site, exfoliation of skin, inflammation at injection site, injection site extravasation, local dryness of skin, skin discoloration at injection site, swelling at injection site [vein]). **Nervous system**: Peripheral motor neuropathy (4%; severe; mainly distal extremity weakness). **Neuromuscular and skeletal**: Arthralgia (3% to 9%).
Monitoring Parameters	• CBC with differential • Liver function tests ((bilirubin, AST, ALT, alkaline phosphatase; prior to each cycle) • Pregnancy testing • Kidney function • Serum uric acid • Monitor for signs/symptoms of neurosensory symptoms, GI toxicity (eg, diarrhea, stomatitis, enterocolitis, and neutropenic colitis), cutaneous reactions or severe skin toxicity, visual impairment, fluid retention, epiphora, canalicular stenosis, tumor lysis syndrome, and second primary malignancies.
Drug Interactions	***Risk X: Avoid combination*** Abrocitinib, Baricitinib, BCG (Intravesical), BCG Products, Brivudine, Cladribine,

	Dengue Tetravalent Vaccine (Live), Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Fusidic Acid (Systemic), Mumps- Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Poliovirus Vaccine (Live/Trivalent/Oral), Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Typhoid Vaccine, Upadacitinib, Vaccines (Live), Yellow Fever Vaccine. ***Risk D: Consider therapy modification*** Anthracyclines, Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), CYP3A4 Inhibitors (Strong), Deferiprone, Denosumab, Dronedarone, Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Palifermin, Platinum Derivatives, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T Vaccines (Inactivated/Non-Replicating). **Note: Docetaxel is a substrate for CYP 3A4:** Strong inhibitors (e.g Clarithromycin Itraconazole, Ketoconazole, Posaconazole) and inducers (eg. Barbiturates (phenobarbital), Carbamazepine, Phenytoin, Rifampicin) of this enzyme may alter docetaxel pharmacokinetics. Consider a Docetaxel dose reduction of 50% if a strong CYP 3A4 inhibitor cannot be avoided.
Pregnancy and Lactation	**Pregnancy:** Contraindicated. May cause fetal harm. No human-controlled studies. An effective method of contraception should be used during treatment. May alter male fertility. **Lactation:** Not recommended due to the potential for serious adverse reactions.
Administration	**Hazardous agent** (NIOSH 2016 [group 1]): Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. **Administration: IV** • Infuse over 1 hour through nonsorbing polyethylene lined (non-DEHP) tubing. • Vesicant; avoid extravasation. **Preparation of administration:** Dilute for infusion in 250 to 500 mL of NS or D5W in a non-DEHP container (eg, glass, polypropylene, polyolefin) to a final concentration of 0.3 to 0.74 mg/mL. Gently rotate and invert manually to mix thoroughly; avoid shaking or vigorous agitation. **Extravasation management:** If extravasation occurs, stop infusion immediately and disconnect, gently aspirate extravasated solution (do **NOT** flush the line); remove needle/cannula; elevate extremity. Apply warm dry compresses for 20 minutes 4 times daily for 1-2 days. Local injection of hyaluronidase with the application of heat can be used to minimize discomfort and the possibility of tissue damage. A dose of 1–6 ml of 150 U/ml hyaloronidase solution is injected through the existing IV line as 1 ml of hyaluronidase solution for each 1 ml of extravasated drug.

	N.B. Refer to manufacturer PIL for specific considerations**.**
Emetogenicity	**Low emetic risk** (10%–30% frequency of emesis).
Warnings/ Precautions	**Premedication (**to reduce the incidence and severity of hypersensitivity reactions and fluid retention**):** • **For breast, non-small cell lung, gastric, and head and neck cancers** - Premedication consists of an oral corticosteroid, such as dexamethasone 16 mg per day (e.g. 8 mg BID) for 3 days starting 1 day before docetaxel administration, unless contraindicated. - Prophylactic G-CSF may be used to mitigate the risk of hematological toxicities. • **For prostate cancer** The recommended premedication regimen is oral dexamethasone 8 mg, 12 hours, 3 hours, and 1 hour before the docetaxel infusion. **Toxic Deaths** May be due to Enterocolitis and neutropenic enterocolitis, sepsis, or gastrointestinal hemorrhage and could lead to death as early as the first day of onset. Caution is recommended for patients with neutropenia, particularly at risk for developing gastrointestinal complications. Patients should be closely monitored for early manifestations of any symptoms of gastrointestinal toxicity. Risk factors include Docetaxel dose 100 mg/m^2, abnormal baseline liver function, a history of prior platinum-based chemotherapy in non-small cell lung cancer patients. **Hepatic Impairment** Avoid Docetaxel Injection in patients with bilirubin > upper limit of normal (ULN), or to patients with AST and/or ALT >1.5 × ULN concomitant with alkaline phosphatase >2.5 × ULN. Patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of severe neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. **Hematologic Effects** Perform frequent peripheral blood cell counts on all patients receiving Docetaxel Injection. Do not retreat patients with subsequent cycles of Docetaxel Injection until neutrophils recover to a level >1500 cells/mm. Avoid retreating patients until platelets recover to a level >100,000 cells/mm^3. **Hypersensitivity Reactions** Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or fatal anaphylaxis, have been reported in patients premedicated with 3 days of corticosteroids. Monitor patients closely especially during the first and second infusions.

Fluid Retention

Patients should be premedicated with oral corticosteroids prior to each Docetaxel Injection administration to reduce the incidence and severity of fluid retention.

When fluid retention occurs, peripheral edema usually starts in the lower extremities and may become generalized with a median weight gain of 2 kg.

Patients with severe fluid retention such as pleural effusion, pericardial effusion and ascites should be monitored closely.

Patients developing peripheral edema may be treated with standard measures, e.g., salt restriction, oral diuretic(s).

Second Primary Malignancies

Second primary malignancies, notably acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), non-Hodgkin's lymphoma (NHL), and renal cancer, have been reported in patients treated with docetaxel with other anti-cancer treatments.

These adverse reactions may occur several months or years after docetaxel-containing therapy.

Cutaneous Reactions

Localized erythema of the extremities with edema followed by desquamation has been observed.

In case of severe skin toxicity, an adjustment in dosage is recommended.

Patients should be informed about the signs and symptoms of serious skin manifestations and monitored closely.

Permanent treatment discontinuation should be considered in patients who experience Severe cutaneous adverse reactions (SCARs)

Neurologic Reactions

The development of severe peripheral neurotoxicity requires a reduction of dose. Mild to moderate neuro-sensory signs are characterised by paresthesia, dysesthesia or pain including burning. Neuromotor events are mainly characterised by weakness.

Eye Disorders

Cystoid macular edema (CME) has been reported, Patients with impaired vision should undergo a prompt and comprehensive ophthalmologic examination.

If CME is diagnosed, Docetaxel Injection treatment should be discontinued and appropriate treatment initiated.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

Tumor Lysis Syndrome

Patients at risk of tumor lysis syndrome (e.g., with renal impairment, hyperuricemia, bulky tumor) should be closely monitored prior to initiating Docetaxel Injection and periodically during treatment. Correction of

	dehydration and treatment of high uric acid levels are recommended prior to initiation of treatment. **Alcohol Content** The alcohol content in some formulations of Docetaxel Injection may affect the central nervous system and should be considered for patients in whom alcohol intake should be avoided or minimized. **Asthenia** Symptoms of fatigue and weakness may last a few days up to several weeks and may be associated with deterioration of performance status in patients with progressive disease.
Storage and Light Sensitivity	• Store intact vials between 2°C to 25°C. • Protect from bright light. • Solutions diluted for infusion should be used within 4 hours of preparation, including infusion time. N.B. Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• This drug induces low blood cell counts. Avoid infections and bleeding causes. • Follow your routine blood tests during treatment with Docetaxel Injection and administration of corticosteroid exactly as your healthcare provider told you. • Allergic reactions may occur. Tell your doctor if you have developed any cutaneous or breathing symptoms. • Tell your doctor if you have liver problems or if you developed gastrointestinal, neurological, cutaneous (eruptions and desquamation) symptoms during treatment. • This drug may cause fetal harm and may alter male fertility. Tell doctor if you are pregnant or breastfeeding.
Sequence of Administration	• Vesicant. • Cell-cycle-specific. • When combined with Vinorelbine or Topotecan, Docetaxel should be given first for less toxicity. • When combined with Doxorubicin or Ifosfamide, Docetaxel should be given second for less toxicity. • When combined with Fluorouracil, Docetaxel may be given first to avoid antagonism in reverse sequence. • When combined with Oxaliplatin, Docetaxel may be given first for less toxicity. • When combined with Gemcitabine or pemetrexed, Docetaxel may be given second to give synergistic effect.

2. Paclitaxel

Generic Name	Paclitaxel
Dosage Form/ Strengths	Concentrate for solution for Infusion (6mg/ml): 30mg/5ml, 150ml/25ml, 300mg/25ml, 300/50ml
Route of Administration	Intravenous.
Pharmacologic Category	Antineoplastic Agent, Antimicrotubular; Taxane Derivative. ATC Code: L01CD01
Indications	**N.B.** *Refer to literature and specific protocols for all indications.* • **Breast cancer**: Adjuvant treatment of node-positive breast cancer (as sequential therapy following anthracycline-containing combination chemotherapy). • **Kaposi sarcoma (AIDS-related)**: Second-line treatment of AIDS-related Kaposi sarcoma. • **Non-small cell lung cancer**: First-line treatment of non-small cell lung cancer (in combination with cisplatin) in patients who are not candidates for potentially curative surgery and/or radiation therapy. • **Ovarian cancer**: Subsequent therapy for treatment of advanced ovarian cancer; (in combination with cisplatin). • **Primary peritoneal cancer** • **Fallopian tube cancer**
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols.* N**.B. All patients must be premedicated with corticosteroids, antihistamines, and H2 antagonists** prior to treatment with Paclitaxel. **Adult dosing:** • **<u>Breast cancer:</u>** - Adjuvant treatment: 175 mg/m^2 over 3 hours every 3 weeks for 4 cycles (administer sequentially following an anthracycline-containing regimen). - First-line: ▪ 220 mg/m^2 administered intravenously over a period of 3 hours, every 3weeks, 24 hours after doxorubicin 50mg/m^2. ▪ 175 mg/m^2 administered intravenously over a period of 3 hours, every 3weeks, 24 hours in combination with trastuzumab. • **<u>AIDS-related Kaposi sarcoma:</u>** IV: 135 mg/m^2 over 3 hours every 3 weeks or 100 mg/m^2 over 3 hours every 2 weeks (due to dose-related toxicity, the 100 mg/m^2 dose should be used for patients with a lower performance status).

Note: Reduce the dexamethasone premedication dose to 10 mg.

- **Non-small Cell Lung Cancer (NSCLC):**
  135 mg/m^2 over 24 hours every 3 weeks (in combination with Cisplatin).
- **Ovarian cancer, advanced**:
  - Previously untreated (first line): IV: 175 mg/m^2 over 3 hours every 3 weeks (in combination with Cisplatin) or 135 mg/m^2 over 24 hours administered every 3 weeks (in combination with Cisplatin)
  - Previously treated (second line): IV: 135 or 175 mg/m^2 over 3 hours every 3 weeks.

Pediatrics:
Paclitaxel is not to be used in children below 18 years due to lack of data on safety and efficacy.

Dosage Adjustment

N.B. *Refer to protocol used for specific dose modifications.*

- **Dosing: Altered Kidney Function: Adult:**
  No dosage adjustment likely to be necessary for any degree of kidney impairment.
- **Dosing: Hepatic Impairment: Adult:**
  The recommendations are based upon the patient's usual dose (in patients with normal hepatic function) would be 135 mg/m^2 dose over 24 hours or the 175 mg/m^2 dose over 3 hours.

24-hour infusion:

- Transaminases <2 times upper limit of normal (ULN) and bilirubin level ≤1.5 mg/dL: 135 mg/m2
- Transaminases 2 to <10 times ULN and bilirubin level ≤1.5 mg/dL: 100 mg/m2
- Transaminases <10 times ULN and bilirubin level 1.6 to 7.5 mg/dL: 50 mg/m2
- Transaminases ≥10 times ULN or bilirubin level >7.5 mg/dL: Avoid use.

3-hour infusion:

- Transaminases <10 times ULN and bilirubin level ≤1.25 times ULN: 175 mg/m^2
- Transaminases <10 times ULN and bilirubin level 1.26 to 2 times ULN: 135 mg/m^2
- Transaminases <10 times ULN and bilirubin level 2.01 to 5 times ULN: 90 mg/m^2
- Transaminases ≥10 times ULN or bilirubin level >5 times ULN: Avoid use.

- **Dosing: Adjustment for Toxicity: Adult:**
  Reduce dosage by 20% (25% for KS patients) in case of:
  - Severe peripheral neuropathy.
  - **Or** Severe neutropenia (neutrophil <500/mm^3 for a week or longer).

Contra-indications	• Hypersensitivity to Paclitaxel, or any component of the formulation. • Do not initiate or repeat treatment of solid tumors in patients with neutrophil counts <1,500/mm^3 (<1000/mm^3 for Kaposi sarcoma). • Do not initiate or repeat treatment of solid tumors in patients with Platelets counts < 100,000/mm^3 (< 75,000/mm^3 for KS patients).
Adverse Drug Reactions	**Peripheral neuropathy**: Dose related. In severe cases, a dose reduction of 20% (25% for KS patients) is recommended for all subsequent courses of paclitaxel. **>10%** **Cardiovascular**: ECG abnormality (14% to 23%), edema (21%; severe edema: 1%), hypotension (12%) **Dermatologic**: Alopecia (87%) **Gastrointestinal**: Diarrhea (38%), nausea and vomiting (52%), stomatitis (17% to 31%; grade 3/4: ≤3%) **Hematologic & oncologic**: Anemia (47% to 90%; grades 3/4: 2% to 16%), hemorrhage (14%), leukopenia (90%; grade 4: 17%), neutropenia (78% to 98%; grade 4: 14% to 75%), thrombocytopenia (4% to 20%; grades 3/4: 1% to 7%) **Hepatic**: Increased serum alkaline phosphatase (22%), increased serum aspartate aminotransferase (19%) **Hypersensitivity**: Hypersensitivity reaction (31% to 45%; severe hypersensitivity reaction: ≤4%) **Infection**: Infection (15% to 30%) **Local**: Injection-site reaction (13%) **Nervous system**: Asthenia (17%), peripheral neuropathy (42% to 70%; grades 3/4: ≤7%) **Neuromuscular & skeletal**: Arthralgia (≤60%), myalgia (≤60%) **Miscellaneous**: Fever (12%) **1% to 10%** **Cardiovascular**: Bradycardia (3%), cardiac arrhythmia (≤1%; including bigeminy, complete atrioventricular block, ventricular tachycardia [asymptomatic]), hypertension (≤1%), syncope (≤1%), venous thrombosis (≤1%) **Dermatologic**: Changes in nails (2%) **Hematologic & oncologic**: Febrile neutropenia (2%) **Hepatic**: Increased serum bilirubin (7%) **Hypersensitivity**: Anaphylaxis (≤4%), angioedema (≤4%) **Frequency not defined:** **Gastrointestinal**: Peritonitis. **Infection**: Sepsis. **Local**: Erythema at injection site, skin discoloration at injection site, swelling at injection site, tenderness at injection site. **Respiratory**: Pneumonia.

Monitoring Parameters	• CBC with differential and platelet count (frequently). • Liver and kidney function. • Monitor for hypersensitivity reactions, vital signs (frequently during the first hour of infusion). • Continuous cardiac monitoring (patients with conduction abnormalities). • Monitor for signs/symptoms of peripheral neuropathy. • Monitor infusion site during infusion.
Drug Interactions	***Risk* X: Avoid combination** Abrocitinib, Atazanavir, Baricitinib, BCG (Intravesical), Brivudine, Bromperidol, Cladribine, Dengue, Tetravalent Vaccine (Live), Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Fusidic Acid (Systemic), Mumps- Rubella- or Varicella-Containing Live Vaccines, Nadofaragene, Firadenovec, Natalizumab, Pimecrolimus Poliovirus Vaccine (Live/Trivalent/Oral), Ritlecitinib, Ruxolitinib (Topical), Sorafenib,Tacrolimus (Topical), Talimogene, Laherparepvec, Tertomotide Tofacitinib,Typhoid Vaccine, Upadacitinib Vaccines (Live), Yellow Fever Vaccine. ***Risk D: Consider therapy modification:*** Amifostine, Anthracyclines, Coccidioides immitis SkinTest, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), Deferiprone, Denosumab, DOXOrubicin (Conventional), Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Platinum Derivatives, Polymethylmethacrylate Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating).
Pregnancy and Lactation	**Pregnancy:** Paclitaxel can cause fetal harm when administered to a pregnant woman. Female and male patients should use contraceptions for at least 6 months after treatment with Paclitaxel. Paclitaxel produced impairment of fertility in male and female rats. **Lactation**: is not recommended due to the potential secretion into breast milk.
Administration	• **Administration: IV** - Infuse over 3 or 24 hours (depending on indication/protocol). - Infuse through a 0.22-micron in-line filter and polyethylene-lined (non-PVC) administration set. - Premedication is recommended to prevent hypersensitivity reactions. **Extravasation**: Vesicant; avoid extravasation. Ensure proper needle or catheter position prior to administration. **Extravasation Management**: Stop infusion immediately and disconnect (leave cannula/needle in place); gently aspirate extravasated solution (do NOT flush the line); remove needle/cannula; initiate antidote (hyaluronidase) if appropriate; remove needle/cannula; elevate extremity. Apply warm compresses for 20 minutes 4 times daily.

	• **Hazardous agent (NIOSH 2016 [group 1]):** Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. **N.B**. Refer to manufacturer PIL for specific considerations**.**
Emetogenicity	**Pediatrics and Adults:** Low (10% to 30%).
Warnings/ Precautions	**Premedications are recommended as follows** • Dexamethasone 20 mg oral, (approximately 12 and 6 hours, or IV: 30 to 60 min before treatment). • Diphenhydramine (or Chlorpheniramine) 50 mg IV (30 to 60 min before treatment). • Cimetidine 300 mg IV (30 to 60 min prior to treatment). **Severe Myelosuppression** - Severe myelosuppression (primarily neutropenia) is dose-dependent and a dose-limiting toxicity of Paclitaxel. In clinical studies, Grade 3-4 neutropenia occurred in 34% of patients with metastatic breast cancer (MBC), 47% of patients with non-small cell lung. - Cancer (NSCLC) and 38% of patients with pancreatic cancer. - Patients should not be retreated until neutrophils recover to ≥1,500/mm³ (≥ 1,000/mm³ for KS patients) and platelets recover to ≥100,000/mm³ (≥75,000/mm³ for KS patients). In the KS clinical study, most patients were receiving granulocyte colony stimulating factor (G-CSF). **Severe Neuropathy** Sensory neuropathy is dose- and schedule-dependent. If ≥ Grade 3 sensory neuropathy develops, withhold Paclitaxel treatment until resolution to Grade 1 or 2 for metastatic breast cancer or until resolution to ≤ Grade 1 for NSCLC and ovarian cancer followed by a dose reduction for all subsequent courses of Paclitaxel. **Pneumonitis** - Pneumonitis, including some cases that were fatal, occurred in 4% of patients receiving Paclitaxel in combination with gemcitabine and in patients receiving concurrent radiotherapy. - After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with Paclitaxel and gemcitabine. **Severe Hypersensitivity** - Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2 to 4% of patients receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. Conventional Paclitaxel formulations contain polyoxyl 35/polyoxyethylated castor oil (Cremophor EL), which is associated with hypersensitivity

	reactions. Formulations also contain dehydrated alcohol which may cause adverse CNS effects. - All patients should be pretreated with corticosteroids, diphenhydramine, and H2 antagonists. - Patients who experience severe hypersensitivity reactions to Paclitaxel should not be rechallenged with the drug. **Use in Patients with Hepatic Impairment** The exposure and toxicity of Paclitaxel can be increased in patients with hepatic impairment. Closely monitor patients with hepatic impairment for severe myelosuppression. **Severe cardiac conduction abnormalities** Have been reported rarely with single agent paclitaxel. If occured, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with Paclitaxel. **Severe mucositis** may occur rarely. In KS patients, if severe reactions occur, the Paclitaxel dose should be reduced by 25%.
Storage and Light Sensitivity	• Store intact vials between 15°C to 30°C. • Protect from bright light. • Solutions diluted for infusion in D5W, and NS are stable for up to 27 hours at ambient temperature. • Paclitaxel should be dispensed in either glass or non-PVC containers (e.g., Excel/PAB). Use non-polyvinyl (non-PVC) tubing (e.g., polyethylene) to minimize leaching. N.B. Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• Tell your doctor if you have any health problem, hypersensitivity or taking any medcation. • This drug induces low blood cell counts. Avoid infections and bleeding causes. • If you have upset stomach, throwing up, diarrhea, or decreased appetite, talk with your doctor. There may be ways to lower these side effects. • This drug is teratogenic. Avoid pregnancy during administeration. It might produce impairment of fertility in male and female. • It is common to have nerve problems with this drug including numbness, tingling, or burning feeling in your hands or feet. Call your doctor if you have nerve problems that interfere with daily living, or do not go away. • Tell your doctor right away if you have any Signs of high or low blood pressure like very bad headache or dizziness, passing out, or change in eyesight.
Sequence of Administration	• Cell cycle-specific agent. • Irritant with vesicant-like properties. • When combined with Cyclophosphamide, Doxorubicin, or Epirubicin,

	Paclitaxel should be given second for less toxicity. • When combined with Cisplatin or Gemcitabine, Paclitaxel should be given first for less toxicity. • When combined with Pemetrexed or Bleomycin, Paclitaxel may be given second for a synergistic effect. • When combined with Ifosfamide, Paclitaxel may be given second for less toxicity. • When combined with Oxaliplatin or Irinotecan, Paclitaxel may be given first for less toxicity. • When combined with Fluorouracil, Paclitaxel may be given first to avoid antagonism.

B. Vinca Alkaloids

1. Vinblastine

Generic Name	Vinblastine
Dosage Form/ Strengths	Solution for IV injection or infusion: 10mg/10ml
Route of Administration	IV
Pharmacologic Category	Antineoplastic Agent, Antimicrotubular; Vinca Alkaloid ATC code: L01CA01
Indications	**N.B**. *Refer to literature and specific protocols for all indications*. • Hodgkin's disease • Non-Hodgkin's lymphoma (lymphocytic lymphoma, histiocytic lymphoma, advanced mycosis fungoides) • Renal cell carcinoma • Testicular carcinoma • Histiocytosis X • Kaposi's sarcoma • Breast cancer • Choriocarcinoma (Methotrexate-resistant) Other indications: Bladder cancer
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols*. **Dosing for adults, elderly and children**: 6 mg/m^2 once weekly. **For testicular tumours**: Dosage may be increased to 0.2 mg/kg administered on each of two consecutive days every three weeks. The dose-limiting factor is myelosuppression
Dosage Adjustment	**N.B**. *Refer to protocol used for specific dose modifications*. **Dosing: Altered Kidney Function.** No dosage adjustment necessary. **Dosing: Hepatic Impairment.** Excreted principally by the liver. Serum bilirubin >3 mg/dL: Administer 50% of dose
Contra-indications	• Hypersensitivity to the active substance or to any of the excipients. • For intravenous use only. Fatal if given by other routes. • Leucopenic patients or bacterial infection.
Adverse Drug Reactions	Leucopoenia is the most common side effect and dose limiting factor. **Frequency not defined.** **Cardiovascular**: Angina pectoris, cerebrovascular accident, ECG abnormality,

	hypertension (common), ischemic heart disease, limb ischemia, myocardial infarction, Raynaud's phenomenon **Central nervous system:** Decreased deep tendon reflex, depression, dizziness, headache, malaise (common), metallic taste, neurotoxicity (duration: >24 hours), paresthesia, peripheral neuritis, seizure, tumor pain (common), vertigo. **Dermatologic**: Alopecia (common), dermatitis, skin blister, skin photosensitivity (rare), skin rash **Endocrine & metabolic**: Hyperuricemia, SIADH (syndrome of inappropriate antidiuretic hormone secretion) **Gastrointestinal**: Abdominal pain, anorexia, constipation (common), diarrhea, enterocolitis (hemorrhagic), gastrointestinal hemorrhage, intestinal obstruction, nausea (mild), paralytic ileus, stomatitis, toxic megacolon, vomiting (mild) **Genitourinary**: Azoospermia, urinary retention **Hematologic & oncologic**: Anemia, bone marrow depression (common), granulocytopenia or leukopenia (common; nadir: 5 to 10 days; recovery: 7 to 14 days; dose-limiting toxicity), hemolytic uremic syndrome, rectal hemorrhage, thrombocytopenia (recovery within a few days), thrombotic thrombocytopenic purpura **Local**: Local irritation **Neuromuscular & skeletal**: Jaw pain (common), myalgia, ostealgia (common), weakness **Ophthalmic**: Nystagmus **Otic**: Auditory disturbance, deafness, vestibular disturbance **Respiratory**: Bronchospasm, dyspnea, pharyngitis **Miscellaneous**: Radiation recall phenomenon
Monitoring Parameters	• CBC with differential • Liver function test • Serum Bilirubin (Total and Direct) • Serum electrolytes • Serum uric acid • Monitor for signs/symptoms of infections and infusion site.
Drug Interactions	***Risk X: Avoid combination*** Abrocitinib, Baricitinib, BCG (Intravesical), BCG Products, Brivudine, Cladribine, Dengue Tetravalent Vaccine (Live), Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Fusidic Acid (Systemic), Mumps- Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Poliovirus Vaccine (Live/Trivalent/Oral), Ritlecitinib, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Typhoid Vaccine, Upadacitinib, Vaccines (Live), Yellow Fever Vaccine ***Risk D: Consider therapy modification*** Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), Deferiprone, Denosumab, Influenza Virus Vaccines, Leflunomide, Lenograstim, Coccidioides immitis Skin Test, COVID-19 Vaccine

	(Adenovirus Vector), COVID-19 Vaccine (mRNA), Deferiprone, Denosumab, Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating). **Notes:** • Combined treatment with vinblastine, bleomycin, and cisplatin, there have been reports of nephrotoxicity, pulmonary toxicity, neurotoxicity, ototoxicity, azoospermia, Raynaud's phenomenon, hypertension, and other vascular events (such as myocardial infarction and cerebrovascular accident). • Erythromycin may increase the toxicity of vinblastine which may cause increased severity of neutropenia, myalgia and constipation.
Pregnancy and Lactation	**Pregnancy**: Avoid. Vinblastine may cause fetal toxicity when administered to pregnant women. No adequate and controlled human studies. **Lactation**: Insufficient data, avoid due to potential for serious adverse reactions.
Administration	**Note**: For IV use only; fatal if administered by other routes. **IV injection**: over one minute. **IV infusion**: May dilute dose in 25 to 50 mL NS, LR, or D5W; dilution in larger volumes (≥100 mL) of IV fluids or longer periods is not recommended to avoid extravasation. **Extravasation**: Vinblastine is vesicant; ensures proper needle or catheter placement before and during infusion. Extravasation may cause significant irritation. **Extravasation management**: If this occurs, the injection should be discontinued immediately, and any remaining portion of the dose should be introduced into another vein. Apply warm dry compresses for 20 minutes 4 times daily for 1-2 days. Local injection of hyaluronidase with the application of heat can be used to minimize discomfort and the possibility of tissue damage. A dose of 1–6 ml of 150 U/ml hyaloronidase solution is injected through the existing IV line as 1 ml of hyaluronidase solution for each 1 ml of extravasated drug. **Hazardous agent** (NIOSH 2016 [group 1]): Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. N.B. Refer to manufacturer PIL for specific considerations.
Emetogenicity	• Minimal emetic risk (<10% frequency of emesis). • An individualized approach is appropriate for premedication with antiemetics as needed.
Warnings/ Precautions	• **Bone marrow suppression**: Leukopenia commonly occurs; granulocytopenia may be severe with higher doses. The nadir generally occurs 5 to 10 days after administration; recovery typically occurs 7 to 14 days later.

	• **Neurotoxicity**: May rarely cause disabling neurotoxicity; usually reversible particularly with higher than recommended doses and/or when administered more frequently than recommended. • **Vestibular and auditory damage** to the eighth cranial nerve occur rarely with vinca alkaloids. Symptoms include partial or total deafness, which may be reversible or not, and difficulties with balance. Caution when used in combination with other ototoxic agents, such as the platinum-containing oncolytic. • **Pulmonary toxicity**: Acute shortness of breath and severe bronchospasm have been reported, most often in association with concurrent administration of mitomycin; may occur within minutes to several hours following vinblastine administration or up to 14 days following mitomycin administration; use caution in patients with preexisting pulmonary disease. • For IV use only, fatal if administered by other routes.
Storage and Light Sensitivity	• Store intact vials at 2°C to 8°C. • Protect from light. N.B. Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• Call your doctor if you have signs of infection, Hearing problems, high blood pressure, Shortness of breath, constipation, or Nerve problems. • Pregnancy should be avoided during administration with Vinblastine.
Sequence of Administration	• Cell cycle specific (M and S phases). • Vesicant. • Vesicant and cell cycle-specific are given first.

2. Vincristine

Generic Name	Vincristine
Dosage Form/ Strengths	Solution for injection 1mg/ml, 2mg/2ml Lyophilized Powder 1mg
Route of Administration	IV
Pharmacologic Category	Antineoplastic Agent, Antimicrotubular, Vinca Alkaloid ATC: L01CA02
Indications	***N.B.*** *Refer to literature and specific protocols for all indications used.* **Leukaemias**, including acute lymphocytic leukaemia, chronic lymphocytic leukaemia, acute myelogenous leukaemia and blastic crisis of chronic myelogenous leukaemia. **Malignant lymphomas**, including Hodgkin's disease and non-Hodgkin's lymphomas. **Multiple myeloma.** **Solid tumours**, including breast carcinoma, small cell bronchogenic carcinoma, head and neck carcinoma and soft tissue sarcomas. **Paediatric solid tumours**, including Ewing's sarcoma, embryonal rhabdomyosarcoma, neuroblastoma, Wilms' tumour, retinoblastoma and medulloblastoma. **Idiopathic thrombocytopenic purpura**. Patients with true ITP refractory to splenectomy and short-term treatment with adrenocortical steroids. **Other indications**: Central nervous system tumors and Thymomas.
Dosage Regimen	***N.B.*** *Different doses and regimens have been used; consult the literature for specific protocols****.*** **Adults**: 1.4 to 1.5 mg/m^2 at weekly intervals up to a maximum weekly dose of 2 mg. **Children**: 1.4 to 2 mg/m^2 given on a weekly basis with a maximum weekly dose of 2 mg. For children weighing 10 kg or less the starting dose should be 0.05 mg/kg administered as a weekly intravenous injection.
Dosage Adjustment	***N.B.*** *Refer to the protocol used for specific dose modifications.* - **Dosing: Altered Kidney Function: Adult** No dosage adjustment is necessary. - **Dosing: Hepatic Impairment: Adult** Serum bilirubin >3 mg/dL: Administer 50% of normal dose. Neuromuscular toxicities may require dose reduction.
Contra-indications	• Patients with the demyelinating form of Charcot-Marie-Tooth syndrome. • Hypersensitivity to vincristine sulfate or to any of the excipients.

	• Fatal if given by any other route than intravenous.
Adverse Drug Reactions	• Most common: Hair loss, neuromuscular symptoms, paralytic ileus. • Short time and reversible: Neuritic pain, constipation, and Leukopenia (less likely than other oncolytic agents). **Dermatology/skin:** Extravasation results in pain and cellulitis, necrosis, alopecia (20-70%), oedema **Auditory/Hearing:** Dizziness, hearing impairment (temporary or permanent), vertigo **Neurology:** Peripheral neuropathy (most common side effect), jaw pain, constipation, paralytic ileus, motor difficulties. **Endocrine**: Syndrome of inappropriate antidiuretic hormone (rare) **Gastrointestinal:** Abdominal cramps, stomatitis, diarrhea, oral ulceration.
Monitoring Parameters	• CBC with differential. • Neurologic function. • Liver function test, Serum bilirubin (total and direct). • Serum uric acid
Drug Interactions	***Risk X: Avoid combination*** Fexinidazole, Fusidic Acid (Systemic) ***Risk D: Consider therapy modification*** Strong CYP3A4 Inhibitors (e.g. Clarithromycin, Itraconazole, Ketoconazole, Posaconazole), Lenograstim, Lipegfilgrastim, Palifermin, Phenytoin. **Note** In combination with L-asparaginase: Vincristine should be given 12 to 24 hours before administration of L-asparaginase to minimize toxicity, since administering L-asparaginase first may reduce hepatic clearance of vincristine.
Pregnancy and Lactation	**Pregnancy**: Avoid. Vincristine can cause fetal harm when administered to a pregnant woman. Use effective contraception during administration and after last dose with several months. **Lactation**: Insufficient data, avoid due to possible risk.
Administration	**N.B. For IV use only, fatal if given by any other route**. Must be labelled “Not for intrathecal”. **Hazardous agent** (NIOSH 2016 [group 1]): Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. **Direct IV injection** over one minute. **IV Infusion**: over 5 to 10 minutes after dilution in a 50 ml NS or dextrose. After administration the vein must be flushed through thoroughly. **Extravasation**: Vincristine is vesicant. Care should be taken to avoid extravasation as this may cause local ulceration. **Extravasation management**: Vincristine should be discontinued immediately if extravasation occured. Use a separate vein to complete administration. Apply

	warm dry compresses for 20 minutes 4 times daily for 1-2 days. Local injection of hyaluronidase with the application of heat can be used to minimize discomfort and the possibility of tissue damage. A dose of 1–6 ml of 150 U/ml hyaloronidase solution is injected through the existing IV line as 1 ml of hyaluronidase solution for each 1 ml of extravasated drug. N.B. Refer to manufacturer PIL for specific considerations**.**
Emetogenicity	**Minimal emetic risk:** <10% frequency of emesis
Warnings/ Precautions	• **Gastrointestinal effects**: Constipation, paralytic ileus, intestinal necrosis and/or perforation may occur; constipation responds well to enemas and laxatives. All patients should be on a prophylactic bowel management regimen as increased fiber in diet. • **Neurotoxicity**: Include alterations in mental status such as depression, confusion, or insomnia; neurologic effects may require dosage reduction. Use with caution in patients with elderly, pre-existing neuromuscular disease, with concomitant neurotoxic agents and/or spinal cord irradiation. • **Respiratory effects**: Acute shortness of breath and severe bronchospasm have been reported with vinca alkaloids, usually when used in combination with mitomycin. Onset may be several minutes to hours after vincristine administration and up to 2 weeks after mitomycin. Progressive dyspnea may occur. Do not re-administer Vincristine. • **Uric acid nephropathy**: Acute uric acid nephropathy has been reported with vincristine. • **Hepatic impairment**: Use with caution in patients with hepatic impairment. Vincristine may be associated with hepatic sinusoidal obstruction syndrome (formerly called veno-occlusive disease). Vincristine has produced severe hepatic toxicity when given in conjunction with abdominal radiation therapy. • Vincristine sulfate penetrates the blood-brain barrier poorly, so additional agents may be required for central nervous system leukemias. • **For IV use only:** For IV administration only; fatal if given by other routes. • **Folinic acid** has been observed to have a protective effect which were administered lethal doses of vincristine
Storage and Light Sensitivity	• Stored at 2-8ºC. • Diluted products in NS and protected from light are stable for up to 24 hours at 2 to 8 °C and only 8 hours at 25 °C and normal light. • Light sensitive, protect from light. **N.B.** Refer to manufacturer PIL for specific considerations**.**
Patient Counselling Keys	• This drug may cause tissue damage if the drug leaks from the vein. Tell your nurse if you have any redness, burning, pain, or leaking of fluid. • Get medical help right away if you have any of the following signs: burning, numbness, or tingling feeling, signs of an allergic reaction, muscle weakness, shortness of breath, seizures, severe constipation, or stomach pain.

	• To help with constipation, you may need to drink more liquids, exercise, or include more fiber in your diet. • This medication is teratogenic. Use effective contraception during administration and after last dose with several months.
Sequence of Administration	• Vesicant • Cell cycle specific • Vesicant and cell cycle-specific are given first.

3. Vinorelbine

Generic Name	Vinorelbine
Dosage Form/ Strengths	Concentrate for Solution For I.V Infusion: 10 mg/ml, 50mg/5ml Capsule: 20mg, 30mg
Route of Administration	IV, Oral
Pharmacologic Category	Antineoplastic Agent, Antimicrotubular, Vinca Alkaloid ATC: L01CA04
Indications	***N.B.*** *Refer to literature and specific protocols for all indications used* • Breast cancer, metastatic in which chemotherapy with anthracycline and taxane has failed or is inadequate. • Non-small cell lung cancer, metastatic or locally advanced (as monotherapy and in combination with cisplatin). **Other indications:** Hodgkin lymphoma, Cervical cancer, Malignant pleural mesothelioma, Ovarian cancer, Salivary gland cancer, Soft tissue sarcoma
Dosage Regimen	***N.B.*** *Different doses and regimens have been used; consult the literature for specific protocols.* **Adult**: ***Intravenous***: **Non-small cell lung cancer or Metastatic breast cancer:** **Usual dose**: 25-30 mg/m² once weekly. **For non- small cell lung cancer, as combination therapy**: frequency of administration is reduced e.g. day 1 and 5 every 3 weeks or day 1 and 8 every 3 weeks according to treatment protocol. **Maximum tolerated dose** per administration: 35.4 mg/m² or 60 mg. ***Oral***: Initial 60mg/m² once weekly for 3 weeks then increase to 80mg² once weekly (only if neutrophil has not fallen during the initial treatment below 500/mm³ or more than once between 500 and 1000/mm³). **Maximum Oral tolerated dose**: 120 mg per week (at 60 mg/m²) and 160 mg per week (at 80 mg/m²) **Switching route:** The oral dose of 80 mg/m² was demonstrated to correspond to 30 mg/m² of the IV form and 60 mg/m² to 25 mg/m².

	The primary dose-limiting toxicity is neutropenia. **N.B**. If the neutrophil count is below 1000 /mm^3 and/or the platelet count below 100000/mm^3, then the treatment should be delayed until recovery. **Pediatrics**: Not recommended. The safety and efficacy in children and adolescents have not been demonstrated and administration is therefore.
Dosage Adjustment	***N.B.*** *Refer to the protocol used for specific dose modifications.* **Dosing: Altered Kidney Function: Adult** No dosage adjustment is necessary. **Dosing: Hepatic Impairment: Adult** Severe liver impairment: Not recommended. May give 20mg/m^2 and close monitoring of hematological parameters. **Dosage in myelosuppression:** When neutrophil count between 1000 and 1500/mm^3: adjust dose to 50%. Neutrophil count < 1,000/mm^3: Contraindicated.
Contra-indications	• Hypersensitivity to the active substance or other vinca alkaloids, or to any of the excipients • Neutrophil count < 1,000/mm^3 or severe current or recent infection (within the last 2 weeks). • Thrombocyte count below 100,000/mm^3 and severe hepatic insufficiency may be considered as contraindication.
Adverse Drug Reactions	**>10%** **Central nervous system**: Neurotoxicity (44%), peripheral neuropathy (20%; grades 3/4: 1%). **Dermatologic**: Alopecia (12% to 30%). **Gastrointestinal**: Nausea (≤34%), vomiting (≤31%), constipation (29%), diarrhea (12% to 13%). **Hematologic & oncologic**: Neutropenia (80% to 85%; grades 3/4: 29% to 69%), leukopenia (81% to 83%; grades 3/4: 12% to 32%), anemia (77%; grades 3/4: 1% to 9%). **Hepatic**: Increased serum aspartate aminotransferase (54%). **Local**: Injection site reaction (22% to 38%; includes erythema at injection site, vein discoloration), pain at injection site (13%). **Neuromuscular & skeletal**: Asthenia (27%). **Renal**: Increased serum creatinine (13%). **1% to 10%** **Cardiovascular**: Localized phlebitis (10%), chest pain (5%). **Central nervous system**: Neuropathy (grades 3/4: 1%). **Hematologic & oncologic**: Febrile neutropenia (≤8%), thrombocytopenia (3% to 4%; grades 3/4: 1%). **Hepatic**: Increased serum bilirubin (9%).

	Infection: Sepsis (≤8%). **Otic**: Ototoxicity (1%). **Respiratory**: Dyspnea (3%).
Monitoring Parameters	• CBC with differential • Liver function test • Pregnancy testing • Monitor for pulmonary symptoms; neuropathy; constipation. • Monitor infusion site.
Drug Interactions	***Risk X: Avoid combination*** Abrocitinib, Baricitinib, BCG (Intravesical), BCG Products, Brivudine, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib Mumps- Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Poliovirus Vaccine (Live/Trivalent/Oral), Ritlecitinib, Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Typhoid Vaccine, Upadacitinib, Vaccines (Live), Yellow Fever Vaccine. ***Risk D: Consider therapy modification*** Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), Deferiprone, Denosumab, Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating). **N.B**. Interactions with strong inhibitors or inducers of CYP3A4: Caution must be exercised. Combination with Phenytoin (like all cytotoxics) and with Itraconazole (like all vinca alkaloids) is not recommended.
Pregnancy and Lactation	**Pregnancy**: Contraindicated. Vinorelbine may cause fetal harm if administered during pregnancy. Patients should use effective contraception during vinorelbine treatment and for 3- 6 months after discontinue therapy. Risk of irreversible fertility for men. **Lactation**: Not recommended due to the potential for serious adverse reactions in the breastfed infant.
Administration	**Hazardous agent** (NIOSH 2016 [group 1]): Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. If the solution contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water. Avoid contact with eye. **Route of administration:** Vinorelbine must only be administered by the intravenous route. The use of intrathecal route is contra-indicated. **IV Slow bolus injection:** (6-10 minutes) after dilution in 20-50 ml NS (0.9 %) or in 5 % (w/v) dextrose solution for injection **Short infusion** (20-30 minutes) after dilution in 125 ml NS (0.9 %) or 5 % (w/v) dextrose solution for injection.

	Administration should always be followed by NS or D5W infusion with at least 125-250 ml to flush the vein. **Extravasation**: Vinorelbine is vesicant and must be administered intravenously with care to avoid extravasation and local irritation. If extravasation occurred, infusion must be stopped immediately, the vein flushed through with sodium chloride (0.9 %) solution and the rest of the dose should be administered in another vein. **Extravasation management:** Apply warm dry compresses for 20 minutes 4 times daily for 1-2 days. Local injection of hyaluronidase with the application of heat can be used to minimize discomfort and the possibility of tissue damage. A dose of 1–6 ml of 150 U/ml hyaloronidase solution is injected through the existing IV line as 1 ml of hyaluronidase solution for each 1 ml of extravasated drug. **Oral**: Swallow whole with water, without chewing, or dissolving the capsule. It is recommended to administer the capsule with some food. N.B. Refer to manufacturer PIL for specific considerations**.**
Emetogenicity	• Minimal emetic risk (<10% frequency of emesis).
Warnings/ Precautions	• **Bone marrow suppression**: Fatal severe myelosuppression may occur. Neutropenia, thrombocytopenia, and anemia may occur with vinorelbine; neutropenia is the major dose-limiting toxicity (grade 3 or 4 neutropenia has commonly occurred). Neutropenia may result in hospitalization (for fever) and/or sepsis. The neutrophil nadir occurs between 7 to 10 days after administration, and recovery occurs within the following 5 to 7days. • **Hepatic impairment:** Drug-induced liver injury (elevated AST and bilirubin) occur in patients receiving Vinorelbine injection. If there is significant hepatic impairment the dose should be reduced. Caution and careful hematological monitoring are necessary. Vinorelbine should not be given concomitantly with radiotherapy if the treatment field includes the liver. • **Pulmonary toxicity:** including bronchospasm – especially if used concomitantly with mitomycin C. Appropriate precautionary measures should be considered. Patients should be informed that they should contact the physician in case of dyspnea. • **Neuropathy**: Sensory and motor neuropathies may occur; may be severe. Usually reversible after discontinuation. Signs/symptoms of neuropathy include paresthesia, hyperesthesia, hyporeflexia, and muscle weakness. prior treatment with paclitaxel may result in cumulative neurotoxicity. • **GI toxicity**: Severe and fatal paralytic ileus, constipation, intestinal obstruction, necrosis, and perforation may occur with vinorelbine. Begin a prophylactic bowel regimen (including adequate dietary fiber intake, hydration, and routine

	stool softeners) to minimize potential constipation, bowel obstruction and/or paralytic ileus. • **Vomiting**: Vinorelbine soft capsule is associated with a higher incidence of nausea and vomiting than the IV formulation. Do not re-administer in case of vomiting within a few hours after drug intake. Supportive treatment such as 5HT3 antagonists (e.g. Ondansetron, Granisetron) may reduce the occurrence of this. • Special care should be taken when prescribing for patients with history of ischemic heart disease or poor performance status
Storage and Light Sensitivity	• Store intact vials at 2°C to 8°C; do not freeze. • After dilution may be used for up to 24 hours in polyvinyl chloride bags at 5° to 30°C under normal room light. • Protect from light. N.B. Refer to manufacturer PIL for specific considerations**.**
Patient Counseling Keys	• This drug induces low blood cell counts. Avoid infections and bleeding causes. • Contact your physician if gastrointestinal symptoms occurred. There are ways to lower these side effects. • Call the physician immediately if any of these signs occurred: allergic reaction, infusion leakage, signs of liver problems, Chest pain, infection, bleeding or Muscle weakness. • Avoid getting pregnant or you partner getting pregnant during treatment and after a specific period after final dose. Risk of irreversible fertility for men.
Sequence of Administration	• Vesicant. • Cell cycle specific. • When combined with Gemcitabine, Vinorelbine may be given first to avoid antagonism in reverse sequence.

CYTOTOXIC ANTIBIOTICS

A. Anthracycline Antibiotics

1. Daunorubicin

Generic Name	Daunorubicin
Dosage Form/ Strengths	Lyophilized Powder for IV injection: 20mg
Route of Administration	IV
Pharmacologic Category	Antineoplastic Agent, Anthracycline, Topoisomerase II Inhibitor ATC: L01DB02
Indications	**N.B.** Refer to literature and specific protocols for all indications used. **In combination with other chemotherapy for the treatment of:** **Acute lymphocytic leukemia** (ALL) in children and adults **Acute myeloid leukemia** (AML) in adults
Dosage Regimen	**N.B.** Different doses and regimens have been used; consult the literature for specific protocols. **Notes:** • Dose, frequency, number of doses, and start date may vary by protocol and treatment phase; refer to individual protocols. • Daunorubicin is associated with a moderate emetic potential; antiemetics are recommended to prevent nausea and vomiting. • Monitor cumulative anthracycline dose (combined); the risk for cardiomyopathy increases as the cumulative anthracycline dose increases (≥250 mg/m^2 of doxorubicin isotoxic equivalent dose in pediatric patients <18 years and 550 mg/m^2 of doxorubicin isotoxic equivalent dose in patients ≥18 years); also dependent on other/additional risk factors (eg, chest irradiation); interpatient variability exists (eg, some patients may experience left ventricular dysfunction at lower doses). To calculate doxorubicin equivalent dose of daunorubicin, multiply total daunorubicin dose by 0.5 **Adult dosing:** **Acute lymphocytic leukemia**: **IV:** 45 mg/m^2 on days 1, 2, and 3 (in combination with vincristine, prednisone, and asparaginase). **Acute myeloid leukemia:** Adults <60 years of age: Induction: **IV:** 45 mg/m^2 on days 1, 2, and 3 of the first course of induction therapy; subsequent courses: 45 mg/m^2 on days 1 and 2 (in combination with cytarabine). Adults ≥60 years of age: Induction: **IV:** 30 mg/m^2 on days 1, 2, and 3 of the first course of induction therapy; subsequent courses: 30 mg/m^2 on days 1 and 2 (in combination with cytarabine). **Pediatric dosing: Acute lymphocytic leukemia** Infants and Children <2 years or BSA <0.5 m^2: IV: 1 mg/kg/dose on day 1 every

	week for up to 4 to 6 cycles (in combination with vincristine and prednisone). Children and Adolescents ≥2 years and BSA ≥0.5 m^2: IV: 25 mg/m^2/dose on day 1 every week for up to 4 to 6 cycles (in combination with vincristine and prednisone).
Dosage Adjustment	**N.B.** Refer to the protocol used for specific dose modifications. **Dosing: Altered Kidney Function: Adult and Pediatric** CrCl <30 mL/minute: Administer 50% of the dose. Hemodialysis/continuous ambulatory peritoneal dialysis (CAPD): Administer 50% of dose. **Dosing: Hepatic Impairment: Adult and Pediatric** Serum bilirubin 1.2 to 3 mg/dL: Administer 75% of dose. Serum bilirubin >3 mg/dL: Administer 50% of dose. In case of Serum bilirubin >5 mg/dL: Avoidance of use is recommended
Contra-indications	Hypersensitivity to Daunorubicin or any component of the formulation.
Adverse Drug Reactions	**Extravasation:** Severe local tissue necrosis will occur if extravasation occurred during administration. **Bone marrow suppression:** Severe myelosuppression occurs; this may lead to infection or hemorrhage. **Cardiomyopathy:** Myocardial toxicity, potentially fatal congestive heart failure may occur either during therapy or months to years after termination of therapy. The incidence of myocardial toxicity increases after a total cumulative dose exceeding 400 to 550 mg/m^2 in adults, 300 mg/m^2 in children older than 2 years of age, or 10 mg/kg in children younger than 2 years of age. **>10%** **Cardiovascular**: Cardiac failure (dose-related, may be delayed for 7 to 8 years after treatment), ECG abnormality (transient, generally asymptomatic and self-limiting; includes atrial premature contractions, ST segment changes on ECG, supraventricular tachycardia, ventricular premature contractions) **Dermatologic**: Alopecia (reversible) **Gastrointestinal**: Nausea (mild), stomatitis, vomiting (mild) **Genitourinary**: Red urine discoloration **Hematologic & oncologic**: Bone marrow depression (onset: 7 days; nadir: 10 to 14 days; recovery: 21 to 28 days; primarily leukopenia; anemia, thrombocytopenia) **Miscellaneous**: Radiation recall phenomenon **1% to 10%** **Dermatologic**: Discoloration of sweat **Endocrine and metabolic**: Hyperuricemia **Gastrointestinal**: Abdominal pain, diarrhea, discoloration of saliva, gastrointestinal ulcer **Local**: Post-injection flare **Ophthalmic**: Discoloration of tears

Monitoring Parameters	• CBC with differential and platelet count • Liver and renal function test • ECG, left ventricular ejection function (echocardiography [ECHO] or multigated radionuclide angiography [MUGA] scan) • Monitor for signs/symptoms of extravasation.
Drug Interactions	***Risk X: Avoid combination*** Abrocitinib Baricitinib BCG (Intravesical) Bevacizumab Cladribine Deucravacitinib Dipyrone Fexinidazole Filgotinib Natalizumab Pimecrolimus Poliovirus Vaccine (Live/Trivalent/Oral) Rubella- or Varicella-Containing Live Vaccines Sipuleucel-T Tacrolimus (Topical) Tertomotide Tofacitinib Typhoid Vaccine Upadacitinib Vaccines (Live) Yellow Fever Vaccine ***Risk D: Consider therapy modification*** COVID-19 Vaccine (Adenovirus Vector) (mRNA) Deferiprone Denosumab Influenza Virus Vaccines Leflunomide Lenograstim Lipegfilgrastim Margetuximab Palifermin Polymethylmethacrylate Rabies Vaccine Ropeginterferon Alfa-2b Sipuleucel-T Taxane Derivatives Trastuzumab Vaccines (Inactivated/Non-Replicating)
Pregnancy and Lactation	**Pregnancy**: Fetal harm may be induced based on data from animal reproduction studies. **Lactation**: Due to the potential for serious adverse reactions in the breastfed infant, It is recommended that breastfeeding be discontinued during daunorubicin therapy.
Administration	• **Hazardous** agent (NIOSH 2016 [group 1]). • Parenteral IV: Administration rate/technique may vary by protocol. May administer IV push over 1 to 5 minutes into the tubing of a rapidly infusing IV solution of D5W or NS. or may dilute further and infuse over 15 to 30 minutes. Some pediatric protocols use a continuous infusion of the daily dose over 24 hours. • Vesicant; ensure proper needle or catheter placement prior to and during infusion; avoid extravasation. If extravasation occurs, stop infusion immediately and disconnect (leave cannula/needle in place); gently aspirate extravasated solution (do NOT flush the line); remove needle/cannula; elevate extremity. Initiate antidote (IV dexrazoxane). **Preparation for Administration: Adult** • Dilute vials of powder for injection with 4 mL SWFI for a final concentration of 5 mg/mL. May further dilute solution or reconstituted daunorubicin solution in D5W or NS for infusion. • **N.B**. Refer to manufacturer PIL for specific considerations.
Emetogenicity	• Daunorubicin is associated with a moderate emetic potential; antiemetics are recommended to prevent nausea and vomiting.
Warnings/ Precautions	***Concerns related to adverse effects:*** • Bone marrow suppression**:** May cause severe bone marrow suppression when used at therapeutic doses; may lead to infection or hemorrhage. Use with caution

	in patients with drug-induced bone marrow suppression (preexisting), unless the therapy benefit outweighs the toxicity risk. Monitor blood counts at baseline and frequently during therapy. • Extravasation: Vesicant; if extravasation occurs, severe local tissue damage leading to ulceration and necrosis, and pain may occur. For IV administration only. NOT for IM or SC administration. Administer through a rapidly flowing IV line**.** Ensure proper needle or catheter placement prior to and during infusion. Avoid extravasation. • Cardiomyopathy: May cause cumulative, dose-related myocardial toxicity; may lead to heart failure. May occur either during treatment or may be delayed (months to years after cessations of treatment). The incidence of myocardial toxicity increases as the total cumulative (lifetime) dosages approach 550 mg/m^2 in adults, 400 mg/m^2 in adults receiving chest radiation, 300 mg/m^2 in children >2 years of age, or 10 mg/kg in children <2 years of age**.** Monitor left ventricular (LV) function (baseline and periodic) with ECHO or MUGA scan; monitor ECG. • Secondary malignancy: Secondary leukemias may occur when used with combination chemotherapy or radiation therapy. ***Disease-related concerns:*** • Hepatic impairment: **Dosage reductions are recommended in patients with hepatic impairment;** significant hepatic impairment may result in increased toxicities. • Renal impairment: **Dosage reductions are recommended in patients with renal impairment;** significant renal impairment may result in increased toxicities. ***Special populations:*** • Older adult: Cardiotoxicity may occur more frequently in elderly patients. Use with caution in patients with impaired renal function and/or poor marrow reserve due to advanced age; dosage adjustment may be necessary. • Pediatric: Infants and children are at increased risk for developing delayed cardiotoxicity; long-term periodic cardiac function monitoring is recommended. • Radiation recipients: Use with caution in patients who have received radiation therapy; reduce dosage in patients who are receiving radiation therapy simultaneously. ***Dosage form specific issues:*** • Formulations (conventional vs liposomal): Use caution when selecting product for preparation and dispensing; indications, dosages, and adverse event profiles differ between conventional daunorubicin hydrochloride solution and daunorubicin liposomal. ***Other warnings/precautions:*** • Experienced physician**:** Should be administered under the supervision of an experienced cancer chemotherapy physician.
Storage	• Lyophilized powder: Store intact vials of powder at 15°C to 30°C. Protect from light. Retain in carton until time of use. • Reconstituted daunorubicin is stable for 24 hours at room temperature or 48

	hours when refrigerated at 2°C to 8°C. Protect reconstituted solution from light. • Protect intact vial and reconstituted solutions from light. **N.B**. Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• This drug induces low blood cell counts. Avoid infections and bleeding causes. • Cardiotoxicity may occur during or long time after discontinuation of treatment. Caution. Increased risk for elderly and pediatrics. • This drug is Carcinogenic. Teratogenic. Emetogenic.
Sequence of Administration	• Cell cycle phase non-specific. • Vesicant

2. Doxorubicin

Generic Name	Doxorubicin
Dosage form/strengths	Solution for I.V Infusion or 10mg, 20mg, 50mg, 200mg Powder for solution: 10mg, 50mg, 150mg
Route of Administration	*IV*
Pharmacologic Category	Antineoplastic Agent, Anthracyclines, Topoisomerase II Inhibitor ATC: L01DB01
Indications	***N.B.*** *Refer to literature and specific protocols for all indications used.* • **Hematology:** acute lymphoblastic leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, Multiple myeloma. • **Breast cancer** • **Metastatic cases** of Ovarian cancer, bone sarcoma, Soft tissue sarcoma, bladder cancer, Wilms tumor, thyroid carcinoma, neuroblastoma, gastric carcinoma, and bronchogenic carcinoma. **Other indications:** Endometrial carcinoma Salivary glands cancer Head and neck. Adrenocortical carcinoma Small cell lung cancer
Dosage Regimen	***N.B.*** *Different doses and regimens have been used; consult the literature for specific protocols.* • <u>As a single agent:</u> 60 to 75 mg/m^2 IV as a single dose or in divided doses on 2-3 consecutive days, repeated every 21 days. • <u>In combination with other chemotherapy agents</u>: ranges from 30 to 75 mg/m^2 IV repeated every 21 to 28 days. • An alternative dosage is 15-20 mg/m^2 IV per week for elderly or immunosuppressant patients. • Intravesical treatment of superficial bladder cancer: 30-50 mg in 25-50 ml of physiological saline per instillation. The solution should remain in the bladder for 1-2 hours. **N.B**. - Cumulative total lifetime dose of Doxorubicin (including other anthracyclines) should not exceed 450-550 mg/m^2 body surface area. - Cumulative doses above 550 mg/m^2 are associated with an increased risk of cardiomyopathy.
Dosage Adjustment	***N.B.*** *Refer to protocol used for specific dose modifications.* **Cardiac Impairment** Discontinue doxorubicin in patients who develop signs or symptoms of cardiomyopathy.

	Hematologic toxicity According to severity, treatment may be delayed or dose to be reduced. **Patients with Renal Impairment** GFR less than 10 ml/min: 75 % of the calculated dose should be administered. **Patients with Hepatic Impairment** Serum bilirubin concentration**:** 1.2 – 3.0 mg/dL: 50% dose reduction 3.1 – 5.0 mg/dL: 75% dose reduction Greater than 5.0 mg/dL: contraindicated, do not initiate, discontinue.
Contra-indications	• Anthracycline hypersensitivity • Severe hepatic impairment • Severe myelosuppression • Severe arrhythmia, heart failure, previous cardiac infarct, acute inflammatory heart disease, or myocardial infarction. • Increased hemorrhagic tendency. • Previous treatment with anthracyclines with maximum cumulative doses
Adverse Drug Reactions	**(>10%)**: alopecia, nausea, and vomiting. **(1-10%)** **Cardiac disorders**: Cardiomyopathy (2%; e.g. decrease of LVEF, dyspnea), ECG changes. **Blood and lymphatic system disorders**: Bone-marrow suppression Gastrointestinal disorders: Nausea, vomiting, mucositis, anorexia, diarrhea **Renal and urinary disorders**: Local reactions (chemical cystitis) might occur at intravesical treatment. **Skin and subcutaneous tissue disorders**: Alopecia
Monitoring Parameters	• CBC with differential • Echocardiogram • Liver and kidney function test • Multi-gated radionuclide angiography (MUGA) • Serum electrolytes • Serum uric acid • Long-term follow-up cardiac evaluations in pediatrics due to risk of delayed cardiotoxicity
Drug Interactions	***Risk X: Avoid combination*** Abrocitinib, Baricitinib, BCG (Intravesical), BCG Products, Bevacizumab, Brivudine, Cladribine, CYP2D6 Inhibitors, CYP3A4 Inducers, CYP3A4 Inhibitors, Dengue Tetravalent Vaccine (Live), Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Fusidic Acid (Systemic), Lasmiditan, Mumps- Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Natalizumab, Pacritinib, P-glycoprotein/ABCB1 Inducers, P-glycoprotein/ABCB1 Inhibitors, P-

	glycoprotein/ABCB1 Inhibitors, Pimecrolimus, Poliovirus Vaccine (Live/Trivalent/Oral), Ritlecitinib, Ruxolitinib (Topical), Talimogene, Laherparepvec, Taurursodiol, Tertomotide, Tofacitinib, Typhoid Vaccine, Upadacitinib, Vaccines (Live) Yellow Fever Vaccine ***Risk D: Consider therapy modification*** Ado-Trastuzumab Emtansine, Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), Deferiprone, Denosumab, Dexrazoxane, Erdafitinib, Fam-Trastuzumab Deruxtecan, Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Margetuximab, Mumps-Rubella- or Varicella-Containing Live Vaccines, Paclitaxel (Conventional), Paclitaxel (Protein Bound), Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Taxane Derivatives,Trastuzumab, Vaccines (Inactivated/Non-Replicating), Zidovudine. **N.B.** Avoid concomitant use with inducers and inhibitors of CYP3A4, CYP2D6, and P-glycoprotein (eg. Amiodarone, Aprepitant, Cimetidine, Ciprofloxacin, Clarithromycin, Diltiazem, Erythromycin, Fluconazole, Grapefruit juice, Itraconazole, Ketoconazole, Posaconazole, Voriconazole, Verapamil, Barbiturates (phenobarbital), Carbamazepine, Corticosteroids, Phenytoin, Rifampicin, St John's wort, Bupropion, Duloxetine, Fluoxetine, Paroxetine, Quinidine, Ritonavir, Sertraline, Terbinafine).
Pregnancy and Lactation	**Pregnancy**: Avoid due to teratogenicity and toxicity in animal studies. **Lactation**: Discontinue drug or breastfeeding taking into consideration importance of drug to mother.
Administration	**Hazardous Drugs Classification**: NIOSH 2016 List: Group 1: Probably carcinogenic to humans: Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. **IV Administeration**: IV bolus over at least 2 to 15 minutes or by continuous infusion. Experts recommend infusing anthracyclines over at least 1 hour to reduce the potential for cardiotoxicity. Administer routine antiemetic prophylaxis prior to treatment. **Extravasation**: Vesicants, irritant and **c**an result in severe local tissue injury and necrosis. **Extravasation management**: Immediately terminate drug. Apply dry cold compresses to the affected area for 20 minutes 4 times daily for 1-2 days. Do not remove the needle until aspirate extravasated fluid. Do not flush the line. Avoid applying pressure to the site. Elevate the extremity. DMSO topical (99%) or Dexrazoxane IV may be used as antidote. **Preparation of Doxorubicin for injection:** Reconstitute lyophilized powder with NS to a final concentration of 2 mg/mL; gently shake until contents are dissolved. May further dilute doxorubicin solution or reconstituted doxorubicin solution in 50 to 1000 mL D_5W or NS for infusion. Doxorubicin must not be mixed with heparin, as this will result in precipitation

	Refer to manufacturer PIL for specific considerations.
Emetogenicity	• High emetic risk: doses > 60 mg/m^2 • Moderate emetic risk: doses < 60 mg/m^2 (maybe high emetogenic in certain patients).
Warnings/ Precautions	**Secondary malignancy**: Acute myelogenous leukemia and myelodysplastic syndrome occur at a higher incidence in patients treated with anthracyclines, including doxorubicin. **Severe myelosuppression** resulting in serious infection, septic shock, requirement for transfusions, hospitalization, and death may occur. **Myocardial damage** may occur including acute left ventricular failure. - Cumulative total lifetime dose of doxorubicin (including other anthracyclines) should not exceed 450-550 mg/m² body surface area. - Cumulative dose should not exceed 250mg/m^2 in children or patients has other potential risk factors of cardiotoxicity e.g. received prior radiation therapy with monitoring of cardiac functions. **Tumor Lysis Syndrome:** Measure levels of blood uric acid, potassium, calcium, phosphate, and creatinine after initial treatment. Hydration, urine alkalinization, and prophylactic allopurinol to prevent hyperuricemia may be beneficial. **Radiation Sensitization and Radiation Recall:** Doxorubicin can increase radiation-induced toxicity to the myocardium, mucosa, skin, and liver. Radiation recall, including cutaneous and pulmonary toxicity, can occur in patients treated with doxorubicin after prior radiation therapy.
Storage and Light Sensitivity	• Store solution vials at 2° to 8°C. • Store powder for reconstitution: at 20°C to 25°C • Reconstituted Doxorubicin is stable for 7 days at room temperature under normal room lighting and for 15 days when refrigerated at 2°C to 8°C • Protect from light. N.B. Refer to manufacturer PIL for specific considerations.
Patient Counseling Keys	• Doxorubicin Injection can cause irreversible myocardial damage. Contact a healthcare provider for symptoms of heart failure during or after treatment. • This drug induces low blood cell counts. Avoid infections and bleeding causes. • Tell your doctor about any medications you take as there are many drug-drug interactions. • Call the doctor if any of these signs appear (e.g. burning or stinging during your infusion bleeding, infections, weakness, or shortness of breath, fast or abnormal heartbeat, muscle weakness or cramps; upset stomach) • Doxorubicin Hydrochloride Injection/for Injection can cause their urine to appear red for 1 to 2 days after administration. • This drug is teratogenic, use effective contraception during treatment.

Sequence of Administration	• Vesicant. • Has cell-cycle specific and non-specific activity. • When combined with Paclitaxel or Docetaxel, Doxorubicin should be given first for less toxicity.
Pharmaco-genomics	• **RARG, Retinoic acid receptor gamma gene:** Consider testing for RARG in all pediatric patients with an indication for doxorubicin. Pediatric patients who are carriers of the RARG rs2229774 A allele should be considered at high risk for anthracycline-induced cardiotoxicity (ACT). (Poor evidence) • **SLC28A3**: Consider genetic testing for the solute carrier (SLC) transporter SLC28A3 rs7853758 A allele variant in all pediatric patients with an indication for doxorubicin. Pediatric patients who are carriers of this variant should be considered to have a lower risk for anthracycline-induced cardiotoxicity (ACT). (Poor evidence) • **UGT1A6**: Consider testing for UGT1A6*4 (rs17863783) in all pediatric patients with an indication for Doxorubicin. Pediatric patients who are carriers of UGT1A6*4 should be considered at high risk for anthracycline-induced cardiotoxicity (ACT). (Poor evidence)

3. Epirubicin

Generic Name	Epirubicin
Dosage Forms/ Strengths	Solution for IV injection\Infusion 2 mg/ml: 10mg, 50mg Lyophilized Powder 10mg
Route of Administration	IV
Pharmacologic Category	Antineoplastic Agent, Anthracycline, Topoisomerase II Inhibitor. ATC: L01DB03
Indications	**N.B.** *Refer to literature and specific protocols for all indications used*. ***Labeled indications:*** **Breast cancer, adjuvant treatment:** Used as a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer. Ovarian, gastric, lung and colorectal carcinomas. Malignant lymphomas, leukaemias and multiple myeloma. Bladder cancer. Small cell lung cancer.
Dosage Regimen	**N.B.** *Different doses and regimens have been used; refer to literature for specific protocols.* **Breast cancer, adjuvant treatment:** Usual dose: **IV:** 100 to 120 mg/m ^{2} per 3- or 4-week treatment cycle as follows: CEF-120 regimen: **IV:** 60 mg/m ^{2} on days 1 and 8 every 28 days for 6 cycles in combination with cyclophosphamide and fluorouracil FEC-100 regimen: **IV:** 100 mg/m ^{2} on day 1 every 21 days for 6 cycles in combination with cyclophosphamide and fluorouracil **Bladder cancer, non–muscle-invasive Intravesical instillation:** 50 or 80 mg as a single instillation (retained for 1 hour) within 6 hours postoperatively after transurethral resection. **Advanced ovarian cancer:** 60-90 mg/m^2 as monotherapy or 50-100 mg/m^2 as combination therapy every 3 weeks. **Gastric cancer:** 60-90 mg/m^2 as monotherapy or 50- mg/m^2 as combination therapy every 3 weeks. **Small cell lung cancer**: 120 mg/m^2 on day 1 every 3 weeks.
Dosage Adjustment	**N.B.** *Refer to the protocol used for specific dose modifications.* **Dosing: Altered Kidney Function: Adult** • *Mild to moderate renal impairment (SCr less than 5 mg/dL):* No dosage adjustments are necessary. • *Severe renal impairment (SCr greater than 5 mg/dL):* Consider lower doses

	of epirubicin. Specific dosage recommendations are not available, but plasma clearance was reduced by 50% in four patients with an S.Cr. of 5 mg/dL or more. **Dosage: Hepatic Impairment: Adult** • Bilirubin 1.2 to 3 mg/dL or AST 2 to 4 times ULN: Administer 50% of recommended starting dose. • Bilirubin >3 mg/dL or AST >4 times ULN: Administer 25% of recommended starting dose. • Severe hepatic impairment (Child-Pugh class C or serum bilirubin >5 mg/dL): Use is contraindicated. **Hematologic toxicity**: • Dosage adjustments for hematologic and non-hematologic toxicities within a cycle of treatment, is based on nadir platelet counts <50,000/mm3, absolute neutrophil counts (ANC) <250/mm3, neutropenic fever, or Grades 3/4 non-hematologic toxicity. Reduce dose of Day 1 in subsequent cycles to 75% of the Day 1 dose given in the current cycle. Delay Day 1 chemotherapy in subsequent courses of treatment until platelet counts are ≥100,000/mm3, ANC ≥1500/mm3, and nonhematologic toxicities have recovered to ≤ Grade 1. • Consider administering a lower starting dose (75-90 mg/m2) for heavily pretreated patients, patients with pre-existing bone marrow depression, or in the presence of neoplastic bone marrow infiltration. For patients receiving a divided dose (Day 1 and Day 8), the Day 8 dose should be 75% of Day 1 if platelet counts are 75,000-100,000/mm3 and ANC is 1000 to 1499/mm3. If Day 8 platelet counts are <75,000/mm3, ANC <1000/mm3, or Grades 3/4 nonhematologic toxicity has occurred, omit the Day 8 dose. ***Non-hematologic toxicity***: Cardiac toxicity: Discontinue epirubicin if signs/symptoms of cardiomyopathy develop. Consider discontinuation if left ventricular ejection fraction decreases or if signs/symptoms of heart failure develop.
Contra-indications	• Severe hypersensitivity to epirubicin, other anthracyclines, anthracenediones, or any component of the formulation • Severe myocardial insufficiency, recent myocardial infarction, or severe arrhythmias • Previous treatment with anthracyclines up to the maximum cumulative dose • Severe persistent drug-induced myelosuppression • Severe hepatic impairment (Child-Pugh class C or serum bilirubin >5 mg/dL)
Adverse Drug Reactions	**Cardiac toxicity:** Congestive heart failure, can occur with Epirubicin. The risk of cardiomyopathy is proportional to the cumulative exposure, with incidence rates from 3.3% at a cumulative dose of 900 mg/m^2. The risk of cardiomyopathy is further increased with concomitant cardiotoxic therapy. Assess heart

function before and regularly during and after treatment with Epirubicin.

Secondary malignancy: Secondary acute myeloid leukemia and myelodysplastic syndrome occur at a higher incidence in patients treated with anthracyclines, including epirubicin.

Extravasation and tissue necrosis: Extravasation of epirubicin may result in severe local tissue injury and necrosis requiring wide excision of the affected area and skin grafting. Immediately terminate the drug and apply ice to the affected area.

Bone marrow suppression: Severe myelosuppression resulting in serious infection, septic shock, requirement for transfusions, hospitalization, and death may occur.

Percentages reported as part of combination chemotherapy regimens.

Cardiovascular: Decreased left ventricular ejection fraction (asymptomatic; delayed: 1% to 2%), cardiac failure (≤2%), atrioventricular block, bradycardia, bundle branch block, cardiac arrhythmia, cardiomyopathy, ECG abnormality, myocarditis, non-specific T wave on ECG, sinus tachycardia, ST segment changes on ECG, tachyarrhythmia, thromboembolism, ventricular premature contractions, ventricular tachycardia
Central nervous system: Lethargy (1% to 46%)
Dermatologic: Alopecia (70% to 96%), skin rash (1% to 9%), skin changes (1% to 5%)
Endocrine & metabolic: Amenorrhea (69% to 72%), hot flash (5% to 39%)
Gastrointestinal: Nausea and vomiting (83% to 92%; grades 3/4: 22% to 25%), mucositis (9% to 59%; grades 3/4: ≤9%), diarrhea (7% to 25%), anorexia (2% to 3%), abdominal pain, esophagitis, neutropenic enterocolitis, stomatitis, toxic megacolon
Genitourinary: Menopause (premature or early)
Hematologic & oncologic: Neutropenia (54% to 80%; grades 3/4: 11% to 67%; nadir: 10 to 14 days; recovery: by day 21), leukopenia (50% to 80%; grades 3/4: 2% to 59%), anemia (13% to 72%; grades 3/4: ≤6%), thrombocytopenia (5% to 49%; grades 3/4: ≤5%), febrile neutropenia (grades 3/4: ≤6%), acute lymphocytic leukemia, acute myelocytic leukemia, myelodysplastic syndrome
Hepatic: Ascites, hepatomegaly, increased serum transaminases
Hypersensitivity: Hypersensitivity reaction
Infection: Infection (15% to 22%; grades 3/4: ≤2%)
Local: Injection site reaction (3% to 20%; grades 3/4: <1%)
Ophthalmic: Conjunctivitis (1% to 15%)
Respiratory: Dyspnea, pulmonary edema
Miscellaneous: Fever (1% to 5%)

Monitoring Parameters	• CBC with differential • ECG or multi-gated radionuclide angiography (MUGA) • Liver function test • Pregnancy testing • If at risk for tumor lysis syndrome, monitor serum uric acid, potassium, calcium, phosphate, and serum creatinine after initial dose.
Drug Interactions	***Risk X: Avoid combination*** Abrocitinib Baricitinib BCG Products Bevacizumab Cimetidine Cladribine Deucravacitinib Dipyrone Fexinidazole Filgotinib Natalizumab Pimecrolimus Poliovirus Vaccine (Live/Trivalent/Oral) Rubella- or Varicella-Containing Live VaccinesRuxolitinib (Topical) Tacrolimus (Topical) TertomotideTofacitinibTyphoid VaccineUpadacitinibVaccines (Live) Yellow Fever Vaccine ***Risk D: Consider therapy modification*** Ado-Trastuzumab EmtansineCOVID-19 Vaccine (Adenovirus Vector) COVID-19 Vaccine (mRNA) Deferiprone Denosumab Influenza Virus Vaccines Leflunomide Lenograstim Lipegfilgrastim Margetuximab Palifermin Polymethylmethacrylate Rabies Vaccine Ropeginterferon Alfa-2b Sipuleucel-T Taxane Derivatives Trastuzumab Vaccines (Inactivated/Non-Replicating)
Pregnancy and Lactation	**Pregnancy**: Pregnancy should be avoided by females of reproductive potential during epirubicin treatment and for at least 6 months after the last dose. **Lactation**: It is not known if Epirubicin is present in human breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended during treatment and for ≥7 days after the last epirubicin dose.
Administration	**Hazardous** agent (NIOSH 2016 [group 1]): Use appropriate precautions for receiving, handling, storage, preparation. **Administration: IV** • Infuse over 15 to 20 minutes or slow IV push; if lower doses due to dose reduction are administered, may reduce infusion time proportionally. Do not infuse over <3 minutes. Infuse into a free flowing IV solution (NS or D_5 W). Avoid the use of veins over joints or in extremities with compromised venous or lymphatic drainage. • Vesicant. Administer drug through a central venous line. **Extravasation management:** If extravasation occurs, stop infusion immediately and disconnect (leave cannula/needle in place); gently aspirate extravasated solution (do NOT flush the line); remove needle/cannula; elevate extremity. Initiate antidote (dexrazoxane or dimethyl sulfate [DMSO]). Apply dry cold compresses for 20 minutes 4 times daily for 1 to 2 days; withhold cooling beginning 15 minutes before dexrazoxane infusion; continue with holding cooling until 15 minutes after infusion is completed.

	Preparation for Administration: Adult IV: Reconstitute lyophilized powder with sterile water for injection (25 mL for the 50 mg vial) to a final concentration of 2 mg/mL. Shake vigorously; may take several minutes for dissolution. May be further diluted with sterile water for injection. **N.B** Refer to manufacturer PIL for specific considerations.
Emetogenicity	Epirubicin is associated with a moderate or high emetic potential (depending on regimen); antiemetics are recommended to prevent nausea and vomiting.
Warnings/ Precautions	***Concerns related to adverse effects:*** • Bone marrow suppression: Severe myelosuppression resulting in serious infection, septic shock, requirement for transfusions, hospitalization, and death may occur. Leukopenia, neutropenia, thrombocytopenia, and anemia may occur. • Cardiac toxicity Myocardial damage, including acute left ventricular failure, can occur with epirubicin. The risk of cardiomyopathy is proportional to the cumulative exposure, with incidence rates from 0.9% at a cumulative dose of 550 mg/m ^{2}, 1.6% at 700 mg/m ^{2}, and 3.3% at 900 mg/m ^{2}. The risk of cardiomyopathy is further increased with concomitant cardiotoxic therapy. •Extravasation: Extravasation of epirubicin may result in severe local tissue injury and necrosis requiring wide excision of the affected area and skin grafting. If extravasation occurs, immediately terminate administration and apply ice to the affected area. • Secondary malignancy: Secondary acute myelogenous leukemia and myelodysplastic syndrome occur at a higher incidence in patients treated with anthracyclines, including epirubicin. The latency period for secondary leukemias may be short (1 to 3 years). • Thromboembolic events: Thrombophlebitis and thromboembolic phenomena (including pulmonary embolism) have occurred; some cases have been fatal. • Tumor lysis syndrome: Epirubicin may cause tumor lysis syndrome (TLS), particularly in patients with rapid tumor proliferation. ***Special populations:*** • Older age: Females ≥70 years of age should be closely monitored for toxicity due to the possibility of decreased epirubicin clearance. • Pediatric: Children may be at increased risk for developing acute and delayed cardiotoxicity; Long-term periodic cardiac function monitoring is recommended. • Radiation recipients: Epirubicin may increase radiation-induced toxicity to the myocardium, mucosa, skin, and liver. Radiation recall, including cutaneous and pulmonary toxicity, may occur in patients who receive epirubicin after prior radiation therapy. ***Other warnings/cautions:*** • Immunizations: Patients should not be immunized with live or live-attenuated

	viral vaccines during or shortly after treatment; Serious or fatal infection may result in immunocompromised patients. Inactivated vaccines may be administered; however, response may be diminished.
Storage and Light Sensitivity	• Solution: Store intact vials at 2°C to 8°C; do not freeze. Protect from light. Discard unused solution from single dose vials within 24 hours of entry. • Lyophilized powder: Store at room temperature of 15°C to 30°C. Reconstituted solutions are stable for 24 hours when stored at 2°C to 8°C or at room temperature. • Intact vial and reconstituted solutions is affected by light exposure. Protect from light. **N.B** Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• This drug induces low blood cell counts. Avoid infections and bleeding causes. • Cardiotoxicity may occur during or long time after discontinuation of treatment. Caution. Increased risk for elderly and pediatrics. • Color of urine will be orange or red for 1 to 2 days after getting this drug. • This drug is Carcinogenic. Teratogenic. Emetogenic.
Sequence of Administration	• Cell cycle non-specific. • Vesicant. • In combinations regimens: Epirubicin is administered before paclitaxel, fluorouracil, cyclophosphamide and ifosfamide.

4. Mitoxantrone

Generic Name	Mitoxantrone
Dosage Forms/ Strengths	Solution for IV injection: 20mg/ 10 ml.
Route of Administration	**IV**
Pharmacologic Category	• Anthracenedione; Antineoplastic Agent, Topoisomerase II Inhibitor. • ATC code: L01DB07
Indications	**N.B.** *Refer to literature and specific protocols for all indications.* • **Metastatic Breast Cancer.** • **Non-Hodgkin Lymphoma.** • **Acute myeloid leukemia** in adults including Myelogenic, promyelocytic, monocytic, and erythroid acute leukemias. • **Chronic myeloid leukemia**: Remission-induction treatment of blast crisis (in combination regimens). • **Prostate cancer**: In combination with corticosteroids for palliation of advanced castrate-resistant or advanced hormone-refractory prostate cancer. • **Multiple sclerosis**: Secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis for reducing neurologic disability and/or the frequency of clinical relapses. Not indicated for the treatment of primary progressive MS.
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols.* **Adult dosing** **Metastatic Breast cancer, Non-Hodgkin's Lymphoma:** **Single Agent Therapy** **IV:** 14 mg/m^2 single dose, repeated at 21-day intervals. **N.B**. Reduced initial dose (12 mg/m^2 or less) may be used in inadequate bone marrow reserves patients. **Combination therapy** **IV**: Initial: 7 to 12 mg/m^2 depending on combinations and frequency of doses. **Subsequent dosing** **If WBC nadir < 1,500 µl or platelet nadir < 50,000 µl:** Decrease by 2 mg/m^2 from prior dose given after recovery. **If WBC nadir < 1,000 µl or platelet nadir < 25,000 µl:** Decrease by 4 mg/m^2 from prior dose given after recovery.

N.B. In metastatic breast cancer, combinations with other cytotoxic agents including Cyclophosphamide and 5-fluorouracil or Methotrexate and Mitomycin C have been shown to be effective. While specific regimens can't be recommended for non-Hodgkin's lymphoma.

Acute Myeloid leukemia

Single Agent Therapy

IV: 12 mg/m^2 daily for five consecutive days (total of 60 mg/m^2).

Combination therapy

- **Induction: IV infusion:** 12 mg/m^2 daily on Days 1 to 3, with Cytarabine 100 mg/m^2 given as a continuous 24-hour infusion on Days 1 till day 7.
- If needed, A second induction course may be given with Mitoxantrone given for 2 days and Cytarabine for 5 days using same levels of dosing.
- **Consolidation: IV continuous infusion:** Mitoxantrone 12 mg/m^2 daily on Days 1 and 2, and Cytarabine, 100 mg/m^2 given as a continuous 24-hour infusion on Days 1 till day 5. The first course of consolidation may be given approximately 6 weeks after the final induction course; the second course is generally administered 4 weeks after the first.
- **Refractory AML**: A single course of Mitoxantrone 6 mg/m^2 as IV bolus, Etoposide 80 mg/m^2 IV for a period of 1 hour, and Cytarabine 1 g/m^2 IV for a period of 6 hours daily for 6 days.

Treatment of blast crisis in (chronic) Myeloid Leukemia

Relapse: 10 to 12 mg/m^2 as a single IV dose daily over 5 consecutive days (total of 50 to 60 mg/m^2).

Advanced-resistant Prostate cancer

- **IV infusion:** 12 to 14 mg/m^2 given as a short intravenous infusion every 3 weeks, in combination with low oral doses of corticosteroids.
- **Cumulative dose for cancer patients** of 140 mg/m^2, either alone or in combinations, should not be exceeded. It has a 2.6% probability of clinical congestive heart failure.

Multiple sclerosis, relapsing, or secondary progressive

IV infusion (short): 12 mg/m^2 that may be repeated every 1-3 months. The maximum lifetime cumulative dose for Multiple sclerosis patients should not exceed 72 mg/m^2.

Pediatric Dosing

Safety and efficacy in pediatrics have not been established.

Dosage Adjustment	**N.B.** Refer to protocol used for specific dose modifications. **Dosing: Altered Kidney Function: Adult** The safety of Mitoxantrone in patients with renal impairment is not established. Mitoxantrone should be used with caution. **Dosing: Hepatic Impairment: Adult** • The safety of Mitoxantrone in patients with hepatic insufficiency is not established. • Dose adjustments may be necessary but insufficient data for specific recommendation. Patients with severe hepatic impairment (bilirubin > 3.4 mg/dL) have an AUC of more than three times greater than that of patients with normal hepatic function.
Contra-indications	• Hypersensitivity to Mitoxantrone or any component of the formulation (Sulphites). • Breastfeeding. • Treatment of multiple sclerosis in pregnant women.
Adverse Drug Reactions	• **Myocardial toxicity:** Congestive heart failure, tachycardia, EKG changes including arrhythmias, chest pain, and asymptomatic decreases in left ventricular ejection fraction have occurred. • **Myelosuppression**. **>10%** **Cardiovascular**: Edema (10% to 30%), cardiac disease (≤18%), cardiac arrhythmia (3% to 18%), ECG changes (≤11%) **Central nervous system**: Pain (8% to 41%), fatigue (≤39%), headache (6% to 13%) **Dermatologic**: Alopecia (20% to 61%), nail bed changes (≤11%) **Endocrine & metabolic**: Menstrual disease (26% to 61%), amenorrhea (28% to 53%), hyperglycemia (10% to 31%), weight gain (≤17%), weight loss (≤17%), increased gamma-glutamyl transferase (3% to 15%) **Gastrointestinal**: Nausea (26% to 76%), vomiting (6% to 72%), diarrhea (14% to 47%), mucositis (10% to 29%; onset: ≤1 week), stomatitis (8% to 29%; onset: ≤1 week), anorexia (22% to 25%), constipation (10% to 16%), gastrointestinal hemorrhage (2% to 16%), abdominal pain (9% to 15%), dyspepsia (5% to 14%) **Genitourinary**: Urinary tract infection (7% to 32%), hematuria (≤11%), urine abnormality (5% to 11%) **Hematologic & oncologic**: Neutropenia (79% to 100%; onset: ≤3 weeks; grade 4: 23% to 54%), leukopenia (9% to 100%), lymphocytopenia (72% to 95%), anemia (≤75%), decreased hemoglobin (≤75%), thrombocytopenia (33% to 39%; grades 3/4: 3% to 4%), bruise (≤11%), febrile neutropenia (≤11%), petechia (≤11%) **Hepatic**: Increased serum alkaline phosphatase (≤37%), increased serum transaminases (5% to 20%)

	Infection: Infection (4% to 60%), sepsis (≤34%), fungal infection (9% to 15%) **Neuromuscular and skeletal**: Weakness (≤24%) **Renal**: Increased blood urea nitrogen (≤22%), increased serum creatinine (≤13%) **Respiratory**: Upper respiratory tract infection (7% to 53%), pharyngitis (≤19%), dyspnea (6% to 18%), cough (5% to 13%) **Miscellaneous**: Fever (6% to 78%) **1% to 10%** **Cardiovascular**: Cardiac failure (≤5%), ischemia (≤5%), decreased left ventricular ejection fraction (≤5%), hypertension (≤4%) **Central nervous system**: Chills (≤5%), anxiety (5%), depression (5%), seizure (2% to 4%) **Dermatologic**: Diaphoresis (≤9%), skin infection (≤5%) **Endocrine & metabolic:** Hypocalcemia (10%), hypokalemia (7% to 10%), hyponatremia (9%), hypermenorrhea (7%) **Gastrointestinal**: Aphthous stomatitis (≤10%) **Genitourinary**: Impotence (≤7%), proteinuria (≤6%), sterility (≤5%) **Hematologic and oncologic:** Granulocytopenia (6%), hemorrhage (5% to 6%), acute leukemia (≤3%; secondary; includes AML, APL) **Hepatic**: Jaundice (3% to 7%) **Infection**: Fungal infection (cutaneous: ≤10%) **Neuromuscular & skeletal**: Back pain (6% to 8%), arthralgia (≤5%), myalgia (≤5%) **Ophthalmic**: Conjunctivitis (≤5%), blurred vision (≤3%) **Renal**: Renal failure (≤8%) **Respiratory**: Rhinitis (10%), pneumonia (≤9%), sinusitis (≤6%)
Monitoring Parameters	• CBC with differential platelet count, and hemoglobin with each dose. • Liver function test. • Electrolytes, Serum uric acid • Baseline evaluation of left ventricular ejection fraction (LVEF) and cardiac signs (by history, physical examination and ECG) for all patients, and prior to each dose for MS patients then yearly after stopping treatment. • Monitor for hypersensitivity reactions; monitor the infusion site for signs of inflammation.

Drug Interactions	***Risk X: Avoid combination:*** Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, Dengue Tetravalent Vaccine (Live), Deucravacitinib, Dipyrone, Etrasimod, Fexinidazole, Filgotinib, Mumps- Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Poliovirus Vaccine (Live/Trivalent/Oral), Ritlecitinib, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Typhoid Vaccine, Upadacitinib, Vaccines (Live), Yellow Fever Vaccine. ***Risk D: Consider therapy modification*** Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), Deferiprone, Denosumab, Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating). **Side notes:** • Concomitant use of potentially cardiotoxic substances (e.g. anthracyclines) increases the risk of cardiac toxicity. • The combination of vitamin K antagonists and cytotoxic agents may result in an increased risk of bleeding. In patients receiving oral anticoagulant therapy, the prothrombin time ratio or INR should be closely monitored while adding or withdrawing treatment with mitoxantrone.
Pregnancy and Lactation	**Pregnancy:** Mitoxantrone can cause fetal harm when administered to a pregnant woman. Potential human teratogen. There are no adequate and well-controlled studies in pregnant women. **Breastfeeding**: significant concentrations in human milk have been reported for 28 days after the last administration. Avoid breast feeding before treatment with Mitoxantrone due to potential for serious adverse reactions in infants.
Administration	**Hazardous agent** (NIOSH 2016 [group 1]): Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. **Administration: IV** • For IV administration only, do not administer intrathecally, subcutaneously, intramuscularly or intra-arterially. Must be diluted prior to use. • **Rate of administration**: Usually administered as a short IV infusion over 5 to 30 minutes; do not infuse over less than 3 to 5 minutes. **Extravasation** • Irritant with vesicant-like properties; ensure proper needle or catheter placement prior to and during infusion; avoid extravasation. • If extravasation occurs, stop infusion immediately and disconnect; gently aspirate extravasated solution (do **NOT** flush the line); remove needle/cannula; it is recommended that intermittent ice packs be placed over the area of extravasation. Elevate extremity. Systemic treatment with

	Dexrazoxane recently proved to be significantly protective against extravasation. Topical DMSO is a treatment option. Apply dry cold compresses for 20 minutes 4 times daily for 1 to 2 days. **Preparation of administration** • **IV**: concentrate should be slowly injected into a free-flowing intravenous infusion of Sodium Chloride 0.9% or 5% glucose solution throughout not less than 3 to 5 minutes • **IV infusion**: Dilute the required volume of Mitoxantrone Injection in 50-100 ml of Sodium Chloride 0.9% or glucose 5%. • Mitoxantrone should not be mixed in the same infusion as other drugs. **N.B**. Refer to manufacturer PIL for specific considerations.
Warnings/ Precautions	**Bone marrow suppression** • Mitoxantrone may lead to severe myelosuppression (at any dose). Mitoxantrone is generally not recommended in patients with preexisting myelosuppression due to prior chemotherapy. • Hematological nadir usually occurs about 10 days after dosing. • Mitoxantrone therapy generally should not be given to patients with baseline neutrophil counts of less than 1,500 cells/mm^3 (except in treatment of acute myeloid leukemia). **Extravasation** • May cause severe local tissue damage if extravasation occurs. Extravasation resulting in burning, erythema, pain, swelling, and skin discoloration (blue) has been reported; may result in tissue necrosis and require debridement for skin graft. **Hypersensitivity** • May contain sodium metabisulfite, which is associated with allergic-type reactions (including anaphylactic symptoms and potentially severe asthmatic episodes). The risk for hypersensitivity is higher in patients with asthma. **Infections** • Patients have a reduced immunological response to infection. Caution. **Myocardial toxicity** • Myocardial toxicity (potentially irreversible and fatal congestive heart failure) may occur either during therapy or months to years after termination of therapy with Mitoxantrone. • This risk increases with cumulative dose. Cumulative doses of 140 mg/m2 have been associated with probability of clinical congestive heart failure. • In cancer patients: Cardiac function should be carefully monitored during treatment. Left-ventricular ejection fraction (LVEF) evaluation is recommended at regular intervals and/or if signs or symptoms of congestive heart failure developed.

	• In multiple sclerosis patients: Evaluation of the left-ventricular ejection fraction (LVEF) is recommended prior to administration of the initial dose of Mitoxantrone and prior to each dose and yearly for up to 5 years after the end of therapy. • Mitoxantrone should not ordinarily be administered to multiple sclerosis patients, with either LVEF of < 50% or a clinically significant reduction in LVEF. • Cardiac toxicity risk increases with preexisting cardiovascular diseas, prior treatment with anthracyclines or prior mediastinal radiotherapy. **Secondary malignancy** • Mitoxantrone increases the risk of developing secondary acute myeloid leukemia or Myelodysplastic Syndrome in patients with cancer and in patients with MS. The risk is increased in patients who are heavily pretreated, with higher doses, and/or with combination chemotherapy or radiotherapy. **Sodium metabisulfite** • May contain sodium metabisulfite; use caution in patients with asthma or a sulfite allergy. **Appropriate administration** • For IV administration only, do not administer subcutaneously, intramuscularly, or intra-arterially. Do not administer intrathecally; may cause serious and permanent neurologic damage. **Blue-green coloration** • May cause urine to turn blue green for 24 hours post infusion; Bluish discoloration of the sclera, skin and nails may also occur. **Immunizations** • Immunization with live virus vaccines (e.g. yellow fever vaccination) increases the risk of infection and other adverse reactions such as vaccinia gangrenosa and generalized vaccinia, in patients with reduced immunocompetence, such as during treatment with Mitoxantrone. • Vaccinate not sooner than 3 months after the last dose of chemotherapy.
Emetogenicity	• Low (10% to 30%)
Storage and Light Sensitivity	• Store intact vials at 15°C to 30°C; do not freeze. • After dilution, the product should be used within 24 hours if stored at 2-8°C. **N.B**. Refer to manufacturer PIL for specific considerations.
Patient Counseling Keys	• This drug lowers blood counts. Avoid causes of infection and bleeding. And check your blood counts regularly as told by doctor. • Do not take vaccinations before talking with your healthcare provider. • Urine color may turn to blue-green color after treatment. • Call your doctor right away if you have cough; chest pain; fast, slow, or

	abnormal heartbeat; swelling in the arms or legs, shortness of breath, or sudden weight gain; or feeling very tired or weak. • This drug may cause tissue damage if the drug leaks from the vein. Tell your nurse if you have any redness, burning, pain, swelling, blisters, skin sores, or leaking of fluid in infusion site.
Sequence of Administration	• Cell-cycle non-specific. • Irritant with vesicant-like properties

B. Other Cytotoxic Antibiotics

1. Bleomycin

Generic name	Bleomycin
Dosage Form/ Strengths	15.000 I.U. Lyophilized Powder Vial
Route of Administration	IV, IM, S.C, Intrapleural
Pharmacologic Category	Antineoplastic Agent, Antibiotic *ATC*: L01DC01
Indications	***N.B**. Refer to literature and specific protocols for all indications used* • Lymphoma (Hodgkin's and non-Hodgkin's lymphoma) • Squamous cell carcinoma • Metastatic germ cell cancer, Testicular Carcinoma. • Malignant pleural effusion
Dosage Regimen	***N.B**. Different doses and regimens have been used; consult the literature for specific protocols* **N.B**. Maximum lifetime cumulative dosage of bleomycin is 400 units intravenous (IV), intramuscular (IM), or subcutaneous. **Hodgkin lymphoma, non-Hodgkin's lymphoma, Testicular tumors and Squamous cell carcinoma:** 10 to 20 units/m^2 given weekly or twice weekly. Improvement of Hodgkin's disease and testicular tumors appears within 2 weeks. In Hodgkin's disease: After a 50% response, a maintenance dose of 1 unit daily or 5 units weekly intravenously or intramuscularly should be given. **Malignant pleural effusion** (Intrapleural): 60 units as a single dose bolus intrapleural injection dissolved in 50 to 100 mL of NS.
Dosage Adjustment	***N.B.** Refer to protocol used for specific dose modifications.* **Dosing: Altered Kidney Function: Adult** CrCl ≥50 mL/minute: No dosage adjustment is necessary. CrCl <50 mL/minute: Reduction of dose is necessary (may reduce to 30-70% of dose according to renal impairment) **Dosing: Hepatic Impairment: Adult** No dosage adjustment required. **Adjustment for Toxicity: Adult** - Pulmonary toxicity: Discontinue until determined not to be drug related. - Diffusing capacity of the lungs for carbon monoxide (DLCO) <30% to 35% of baseline: Discontinue treatment.

Contra-indications	• Bleomycin Hypersensitivity • Idiosyncratic Reaction
Adverse Drug Reactions	**>10%** Cardiovascular: Phlebitis Central nervous system: Pain at tumor sit Dermatologic: Hyperpigmentation (50%), atrophic striae (≤50%), erythema (≤50%), exfoliation of the skin (≤50%; particularly on the palmar and plantar surfaces of the hands and feet), hyperkeratosis (≤50%), localized vesiculation (≤50%), skin rash (≤50%), skin sclerosis (≤50%), alopecia (may be dose-related and reversible with discontinuation), nailbed changes (may be dose-related and reversible with discontinuation) Endocrine & metabolic: Weight loss Gastrointestinal: Stomatitis (≤30%), mucositis (≤30%), anorexia Miscellaneous: Febrile reaction (25% to 50%; acute) **1% to 10%** Dermatologic: Onycholysis, pruritus, thickening of skin Hypersensitivity: Anaphylactoid reaction (including chills, confusion, fever, hypotension, wheezing; onset may be immediate or delayed for several hours; includes idiosyncratic reaction in 1% of lymphoma patients) Neuromuscular & skeletal: Scleroderma (diffuse) Respiratory: Tachypnea (≤5% to 10%), rales (≤5% to 10%), interstitial pneumonitis (acute or chronic: ≤5% to 10%), pulmonary fibrosis (≤5% to 10%), hypoxia (1%)
Monitoring Parameters	• CBC • Pulmonary function tests • Renal and hepatic function test. • Monitor idiosyncratic reaction symptoms e.g. hypotension, mental confusion, fever, chills, and wheezing, especially at first or second dose.
Drug Interactions	***Risk X: Avoid combination*** Brentuximab, Vedotin ***Risk D: Consider therapy modification*** Granulocyte, Colony-Stimulating Factors, Lenograstim, Lipegfilgrastim, Oxygen, Palifermin
Pregnancy and Lactation	**Pregnancy**: There is a potential risk of embryonic and foetal abnormalities. Bleomycin should therefore not be used during the pregnancy, unless it is strictly necessary, particularly during the first trimester. Both male and female patients should take adequate contraceptive measures up to 6 months after the discontinuation of the therapy. Bleomycin therapy may cause irreversible infertility. **Lactation**: Discontinue breast feeding during Bleomycin therapy due to possible

	harmful effect.
Administration	**Hazardous Agent**: NIOSH 2016 List: Group 1: Possibly carcinogenic (IARC Group 2B): Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. Use in pregnant women includes a risk to the fetus (Pregnancy Category D). - **IV:** Administer IV slowly over at least 10 minutes. Avoid fast bolus, because it leads to high risk of lung damage. Monitor for hypersensitivity, particularly following the first 2 doses in patients with lymphoma. - **IM**: Change the injection site regularly. If needed, a local anesthetic can be added to the injection solution, e.g. 1.5-2 mL lidocaine HCl 1%. **Preparation for administration:** - **IV**: reconstitute 15-unit vial with 5 mL with NS for a resultant concentration of 3 units/mL (3 mg/mL); may be further diluted in 200-1,000 mL NS for administration by continuous IV infusion; slower administration may produce less severe pulmonary toxicity. - **IM**: Reconstitute 15-unit vial with 1 to 5 mL of NS. - **Intrapleural**: 60 units dissolved in 50 to 100 mL NS. **N.B**. Refer to manufacturer PIL for specific considerations.
Emetogenicity	Minimal emetic risk (<10% frequency of emesis)
Warnings/ Precautions	**Pulmonary toxicity:** Severe pulmonary toxicity is the most serious side effect, occurring in approximately 10% of treated patients. It usually appears as pneumonitis, and sometimes progresses to pulmonary fibrosis. Elderly and patients receiving more than 400 units total dose are at higher risk of pulmonary toxicity but may appear in young patients and those treated with low doses. **Idiosyncratic reaction:** A severe idiosyncratic reaction consisting of hypotension, mental confusion, fever, chills, and wheezing has been reported in approximately 1% of lymphoma patients treated with bleomycin. **Vascular toxicity** following use of bleomycin, in particular in combination with other antineoplastic agents. **Tumor Lysis Syndrome**: Measure levels of blood uric acid, potassium, calcium, phosphate, and creatinine after initial treatment. Hydration, urine alkalinization, and prophylactic allopurinol to prevent hyperuricemia may be beneficial.
Storage and Light Sensitivity	• Store intact vials at 2°C to 8°C. • Stable for 24 hours in neutral saline at 25°C. • No light sensitivity

	N.B. Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• Call your doctor or get medical help if any of these side effects bother you: severe dizziness or confusion, cough that does not go away, lung, Kidney or liver disorders. • Bleomycin can cause fetal harm. Avoid getting pregnant during bleomycin treatment. This therapy may cause irreversible infertility
Sequence of Administration	• Cell cycle-phase specific drug (G2 phase). • Non-Vesicant. • When combined with Paclitaxel, Bleomycin may be given first for a synergistic effect.

2. Dactinomycin

Generic Name	Dactinomycin
Dosage Forms/ Strengths	Lyophilized Powder for Injection: 500 mcg
Route of Administration	IV
Pharmacologic Category	Antineoplastic Agent, Antibiotic ATC: L01DA01
Indications	**N.B.** *Refer to literature and specific protocols for all indications used.* Dactinomycin is principally used to treat pediatric cancers. In a combination chemotherapy and/or multi-modality treatment regimen, is indicated for: Treatment of Wilms' tumor Childhood rhabdomyosarcoma Ewing's sarcoma Metastatic, non-seminomatous testicular cancer. As a single agent, or as part of a combination chemotherapy regimen: Treatment of gestational trophoblastic neoplasia.
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols.* **Maximum doses** for all ages: IV: 15 mcg/kg or 400 to 600 mcg/m^2 IV daily for 5 days. IV: 45 mcg/kg or 1,250 mcg/m^2 IV as a single dose.
Dosage Adjustment	**N.B.** *Refer to protocol used for specific dose modifications*. **Patients with Hepatic Impairment Dosing** A 50% Dactinomycin dosage reduction has been suggested in patients with hepatic impairment (e.g., any level of elevated hepatic enzymes). **Patients with Renal Impairment Dosing** No dosage adjustments are needed.
Contra-indications	• Hypersensitivity to the active ingredient or any component of the formulation. • Infection.
Adverse Drug Reactions	**Frequency not defined:** **Cardiovascular**: Thrombophlebitis. **Central nervous system**: Fatigue, malaise, peripheral neuropathy. **Dermatologic**: Acne vulgaris, alopecia, cheilitis, dermatitis, erythema multiforme, skin rash, Stevens-Johnson syndrome, toxic epidermal necrolysis. **Endocrine & metabolic**: Growth suppression, hypocalcemia.

	Gastrointestinal: Abdominal pain, anorexia, aphthous stomatitis, constipation, diarrhea, dysphagia, esophagitis, gastrointestinal ulcer, mucositis, nausea, proctitis, vomiting. **Hematologic & oncologic**: Anemia, bone marrow depression, disseminated intravascular coagulation, febrile neutropenia, hemorrhage, leukopenia, neutropenia (nadir: 14 to 21 days), pancytopenia, reticulocytopenia, second primary malignant neoplasm (including leukemia), thrombocytopenia, tumor lysis syndrome. **Hepatic**: Abnormal hepatic function tests, ascites, hepatic failure, hepatic sinusoidal obstruction syndrome, hepatitis, hepatomegaly, hepatotoxicity, severe hepatic disease. **Hypersensitivity**: Hypersensitivity reaction. **Infection**: Infection, sepsis. **Neuromuscular & skeletal**: Myalgia. **Ophthalmic**: Optic neuropathy. **Renal**: Renal function abnormality, renal failure syndrome, renal insufficiency. **Respiratory**: Pneumonitis, pneumothorax. **Miscellaneous**: Fever, radiation recall phenomenon.
Monitoring Parameters	• CBC before each treatment cycle. • liver function tests (eg. AST, ALT, total bilirubin, alkaline phosphatase). • Renal function tests, and electrolytes. • Pregnancy. • Weight. • Monitor for signs/symptoms of secondary malignancy, extravasation, mucocutaneous reactions, and radiation recall.
Drug Interactions	***Risk X: Avoid combination*** Abrocitinib Baricitinib BCG (Intravesical) BCG Products Cladribine Deucravacitinib Dipyrone Fexinidazole Filgotinib Natalizumab Pimecrolimus Poliovirus Vaccine (Live/Trivalent/Oral) Rubella- or Varicella-Containing Live Vaccines Ruxolitinib (Topical) Tacrolimus (Topical) Talimogene Laherparepvec Tertomotide Tofacitinib Typhoid Vaccine Upadacitinib Vaccines (Live) Yellow Fever Vaccine ***Risk D: Consider therapy modification*** COVID-19 Vaccine (Adenovirus Vector) COVID-19 Vaccine (mRNA) Deferiprone Denosumab Influenza Virus Vaccines Leflunomide Lenograstim Lipegfilgrastim Palifermin Polymethylmethacrylate Rabies Vaccine Ropeginterferon Alfa-2b Sipuleucel-T Vaccines (Inactivated/Non-Replicating)
Pregnancy and Lactation	**Pregnancy**: Dactinomycin is classified as FDA pregnancy risk category D. Due to its potential for teratogenesis, dactinomycin should be avoided during pregnancy. **Lactation**: It is not known if dactinomycin or its metabolites are secreted in human milk. Due to the risk of serious adverse reactions in nursing infants, women should discontinue breast-feeding during dactinomycin therapy and for

	14 days after the last dose
Administration	• **Hazardous** agent (NIOSH 2016 [group 1]): Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. • **Parenteral**: May administer undiluted into the side-port of a free flowing IV infusion by slow IVP over a few minutes; or may further dilute and administer as IV infusion over 10 to 15 minutes; Consider a D5W or NS flush before and after a dactinomycin dose to ensure venous patency. Cellulose ester membrane filters may partially remove dactinomycin from solution and should not be used during administration. Avoid extravasation; do not give IM or SC. • Vesicant; ensure proper needle or catheter placement prior to and during infusion; avoid extravasation. **Extravasation management:** If extravasation occurs, stop infusion immediately and disconnect (leave cannula/needle in place); gently aspirate extravasated solution (do **NOT** flush the line); remove needle/cannula; elevate extremity. Apply dry cold compresses for 20 minutes 4 times a day for 1 to 2 days. **Preparation for Administration:** Reconstitute initially with 1.1 mL of preservative-free SWFI to yield a concentration of 500 mcg/mL. Further dilute in D5W or NS to a recommended concentration of >10 mcg/mL. **N.B**. Refer to manufacturer PIL for specific considerations.
Emetogenicity	Dactinomycin is associated with a high emetic potential; antiemetics are recommended to prevent nausea and vomiting.
Warnings/ Precautions	***Concerns related to adverse effects*** • Bone marrow suppression: Severe and fatal myelosuppression (neutropenia, thrombocytopenia, and anemia) may occur. The neutrophil nadir typically occurs 14 to 21 days after administration. Obtain complete blood counts prior to each cycle; delay the next dactinomycin dose if severe myelosuppression has not improved. Based on the severity of myelosuppression and disease state being treated, consider dose reduction in patients with prolonged myelosuppression. • Dermatologic toxicity: Permanently discontinue dactinomycin if a severe mucocutaneous reaction occurs. • Extravasation: Ensure proper needle or catheter placement prior to and during infusion. Avoid extravasation. Apply dry, cold compresses to the site of extravasation for 20 minutes, 4 times per day for 1 to 2 days. Monitor closely; Plastic surgery consultation may be necessary if extravasation occurs. • Hepatotoxicity: Dactinomycin may cause hepatotoxicity; Monitor AST, ALT, alkaline phosphatase, and bilirubin prior to and during dactinomycin therapy. May require therapy interruption, dose reduction, or permanent

	discontinuation (based on the severity of the reaction and disease being treated). • Nephrotoxicity: Renal function abnormalities may occur with dactinomycin; Monitor creatinine and electrolytes frequently during treatment. • Secondary malignancies: The risk of secondary malignancies (including leukemia) is increased with dactinomycin. ***Special populations*** • Radiation therapy recipients: Dactinomycin potentiates the effects of radiation therapy; use with caution in patients who have received radiation therapy. Reduce the dactinomycin dose by 50% in patients who are receiving dactinomycin and concomitant radiation therapy. Combination with radiation therapy may result in increased toxicity (eg, GI toxicity, myelosuppression, or erythema and vesiculation of the skin or buccal and pharyngeal mucosa). Erythema from prior radiation therapy may be reactivated by dactinomycin. Radiation recall risk appears to be highest when administered within 2 months of prior radiation, although the risk can still occur with distant radiation exposure. ***Other warnings/cautions:*** • Dosage expression: Dosage is usually expressed in micrograms. Calculate the dose for obese or edematous patients based on ideal body weight. • Vaccines: Avoid administration of live vaccines before and during dactinomycin treatment.
Storage and Light Sensitivity	• Store intact vials at 20°C to 25°C. Protect from light and humidity. • Recommended final concentrations (>10 mcg/mL) in D5W or NS should be stored for no more than 4 hours from reconstitution to completion of infusion (due to the lack of preservative). • Reconstituted solutions of dactinomycin are a clear, gold-color and are very sensitive to light. Protect from light. • Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• This drug induces low blood cell counts. Avoid infections and bleeding causes. • Liver, renal, and dermal toxicities may occur. Monitor for signs. Call doctor. • Increased toxicity in patients receiving Radiation therapy. • This drug is Carcinogenic. Teratogenic. Emetogenic.
Sequence of Administration	• Cell cycle nonspecific. • Vesicant.

HORMONAL THERAPIES

A. Antiandrogens

1. Abiraterone

Generic name	Abiraterone Acetate
Dosage Form/ Strengths	Tablets 250mg, 500mg
Route of Administration	Oral
Pharmacologic Category	Antineoplastic Agent, Antiandrogen ATC: L02BX03
Indications	**N.B.** Refer to literature and specific protocols for all indications. **Metastatic Prostate cancer** Treatment of metastatic, castration-resistant prostate cancer Treatment of metastatic, high-risk castration-sensitive prostate cancer
Dosage Regimen	**N.B.** Different doses and regimens may have been used; consult the literature for specific protocols **Oral:** 1,000 mg once daily (in combination with prednisone 5 mg once or twice daily)
Dosage Adjustment	**N.B.** Refer to protocol used for specific dose modifications. **Dosing: Altered Kidney Function** No dosage adjustment is necessary. Caution in severe impairment. **Dosage: Hepatic Impairment** • Hepatic impairment ***before*** treatment initiation: Mild (Child-Pugh class A): No dosage adjustment necessary. Moderate (Child-Pugh class B): 250 mg once daily. Permanently discontinue if ALT and/or AST >5 times the ULN or total bilirubin >3 times ULN occur during treatment in patients with baseline moderate hepatic impairment. Severe (Child-Pugh class C): Do not use. • Hepatotoxicity ***during*** treatment: ALT and/or AST >5 times ULN **or** total bilirubin >3 times ULN: Withhold treatment until liver function tests return to baseline or ALT and AST ≤2.5 times ULN and total bilirubin ≤1.5 times ULN, then reinitiate at lower dose, if recurrent hepatotoxicity, repeat with lower dose until 500mg then permanent discontinue. **Dosing: Adjustment for Toxicity** Adrenocortical insufficiency: Increased corticosteroid doses may be required before, during, and after stress. Hepatotoxicity: Refer to "Dosing: Hepatic Impairment". Hypoglycemia (in patients with diabetes): Antidiabetic medication dosage adjustments may be needed. Mineralocorticoid excess (due to CYP17 inhibition): Concomitant administration with corticosteroids reduces the incidence and severity of these adverse events

	(eg. hypertension, hypokalemia, fluid retention). Control BP and correct hypokalemia prior to and during treatment.
Contra-indications	• Hypersensitivity to Abiraterone acetate or any component of the formulation. • Pregnancy.
Adverse Drug Reactions	**>10%** Cardiovascular: Edema (25% to 27%), hypertension (9% to 37%). Endocrine & metabolic: Hot flash (15% to 22%), hyperglycemia (57%), hypernatremia (33%), hypertriglyceridemia (63%), hypokalemia (17% to 30%), hypophosphatemia (24%). Gastrointestinal: Constipation (23%), diarrhea (18% to 22%), dyspepsia (6% to 11%). Genitourinary: Urinary tract infection (7% to 12%). Hematologic & oncologic: Bruise (13%), lymphocytopenia (20% to 38%; grades 3/4: 4% to 9%). Hepatic: Increased serum alanine aminotransferase (11% to 46%), increased serum aspartate aminotransferase (15% to 37%), increased serum bilirubin (7% to 16%) Nervous system: Fatigue (39%), insomnia (14%). Neuromuscular & skeletal: Arthralgia (≤30%), joint swelling (≤30%), myalgia (26%). Respiratory: Cough (7% to 17%), dyspnea (12%), nasopharyngitis (11%), upper respiratory infection (5% to 13%). **1% to 10%** Cardiovascular: Cardiac arrhythmia (7%), cardiac failure (2% to 3%), chest discomfort (≤4%), chest pain (≤4%). Dermatologic: Skin rash (8%). Genitourinary: Groin pain (7%), hematuria (10%), nocturia (6%), urinary frequency (7%) Nervous system: Falling (6%), headache (8%). Neuromuscular & skeletal: Bone fracture (6%). Miscellaneous: Fever (9%).
Monitoring Parameters	• ALT, AST, and bilirubin prior to treatment, every 2 weeks for 3 months and monthly thereafter; if baseline moderate hepatic impairment (Child-Pugh class B), monitor ALT, AST, and bilirubin prior to treatment, weekly for the first month, every 2 weeks for 2 months then monthly thereafter. • Serum potassium (prior to treatment and at least monthly). • Blood Pressure and monitor for fluid retention (prior to treatment and at least monthly). • Blood glucose (in patients with diabetes) during and after discontinuation of Abiraterone therapy. • Monitor closely for signs/symptoms of Adrenocorticoid insufficiency.

Drug Interactions	***Risk X: Avoid combination*** Doxorubicin, Indium 111 Capromab, Pendetide, Mequitazine, Radium Ra 223 Dichloride, Thioridazine. ***Risk D: Consider therapy modification*** CYP3A4 Inducers (Strong), Eliglustat, Gallium Ga 68 PSMA-11, Piflufolastat F18, Spironolactone, Tamoxifen, Phenytoin, Phenobarbital, Carbamazepine, Antimycobacterials, rifamycins (e.g., rifabutin, rifampin, rifapentine).
Pregnancy and Lactation	**Pregnancy**: Patients with partners who could become pregnant should use effective contraception during treatment and for 3 weeks after the last Abiraterone dose. **Lactation**: Abiraterone is not indicated for use in females.
Administration	**Hazardous** agent (NIOSH 2016 [group 1]) : Teratogenic. Use appropriate precautions for receiving handling, storage, preparation, dispensing, transporting, administration, and disposal. **Administration: Oral** Taken orally on an empty stomach (administer at least 1 hour before and 2 hours after any food). **N.B**. Refer to manufacturer PIL for specific considerations.
Emetogenicity	Minimal or low.
Warnings/ Precautions	***Concerns related to adverse effects:*** • Adrenocortical insufficiency: Adrenocortical insufficiency has been reported rarely. Increased corticosteroid doses may be required before, during, and after stress. • Hepatotoxicity: Severe hepatotoxicity has been reported generally occurring in the first 3 months of treatment. • Mineralocorticoid excess: Increased mineralocorticoids due to CYP17 inhibition may result in hypertension, hypokalemia, and fluid retention. Concomitant administration with corticosteroids reduces the incidence and severity of these adverse events. ***Disease-related concerns:*** • Cardiovascular disease: May cause hypertension, hypokalemia, and fluid retention. Monitor patients with cardiovascular disease at least monthly, particularly those with heart failure, recent MI, or ventricular arrhythmia. • Diabetes: Use with caution in patients with diabetes; Severe hypoglycemia has been reported, particularly in patients receiving concomitant therapy with thiazolidinediones (eg, pioglitazone) or repaglinide. Antidiabetic medication dosage adjustments may be needed. ***Concurrent drug therapy issues:*** • Radium Ra 223 dichloride: Due to an increased risk of fractures and mortality, the

	use of abiraterone plus a corticosteroid in combination with radium Ra 223 dichloride is not recommended.
Storage and Light Sensitivity	Store at between 15°C and 30°C. No precautions needed for light protection. **N.B**. Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• This drug may cause of hypertension, hypercholesterolemia, abnormal heartbeat, electrolyte problems (e.g. hypokalemia), liver toxicity, allergic reaction, UTI infection or a weak adrenal gland. Monitor for symptoms. Refer to doctor. • Monitor blood sugar frequently. Increased risk of hyperglycemia. • To minimize gastric irritation, advise patient to take corticosteroid immediately after food. Consider the use of a H2 antagonist or proton pump inhibitor if appropriate. • Missed doses should not be replaced; if a dose is forgotten or vomited, normal dosing should be resumed at the next scheduled dose. • Interaction with some common medicines e.g Carbamazepine, phenobarbital, phenytoin, rifampicin. • This drug is Carcinogenic. Teratogenic.

2. Bicalutamide

Generic Name	Bicalutamide
Dosage Form/Strengths	Tablets: 50mg, 150mg.
Route of Administration	Oral
Pharmacologic Category	Antineoplastic Agent, Antiandrogen. ATC: L02BB03
Indications	**N.B.** *Refer to literature and specific protocols for all indications.* **Prostate cancer, metastatic:** Treatment of stage D $_2$ metastatic prostate cancer (in combination with a luteinizing hormone-releasing hormone (LHRH) analog) ***Other indications:*** Prostate cancer, locally advanced, high recurrence risk
Dosage Regimen	**N.B.** *Different doses and regimens may have been used; consult the literature for specific protocols.* **Adult: Prostate cancer, metastatic: Oral:** 50 mg once daily Continue until disease progression or unacceptable toxicity (if used for preventing tumor flare, for 4 to 6 weeks) **Prostate cancer, locally advanced, high recurrence risk (off-label use): Oral:** 150 mg once daily (as monotherapy)
Dosage Adjustment	**N.B.** *Refer to protocol used for specific dose modifications*. **Dosing: Altered Kidney Function** No dosage adjustment is necessary. **Dosage: Hepatic Impairment** No dosage adjustment is necessary. Jaundice, or ALT greater than 2 times the upper limit of normal: Discontinue Bicalutamide treatment.
Contra-indications	• Hypersensitivity to Bicalutamide or any component of the formulation. • Use in women.
Adverse Drug Reactions	**>10%** **Cardiovascular**: Peripheral edema (13%). **Central nervous system**: Pain (35%). **Endocrine & metabolic**: Hot flash (53%), gynecomastia (9%; monotherapy [150 mg]: 38% to 73%). **Gastrointestinal**: Constipation (22%), nausea (15%), diarrhea (12%), abdominal pain (11%). **Genitourinary**: Mastalgia (6%; monotherapy [150 mg]: 39% to 85%), pelvic pain (21%), haematuria (12%), nocturia (12%). Hematologic & oncologic: Anemia (11%).

	Infection: Infection (18%). Neuromuscular & skeletal: Back pain (25%), weakness (22%). Respiratory: Dyspnea (13%). **≥2% to 10%** **Cardiovascular**: Chest pain (8%), hypertension (8%), angina pectoris (<5%), cardiac arrest (<5%), cardiac failure (<5%), coronary artery disease (<5%), edema (<5%), myocardial infarction (<5%), syncope (<5%). **Central nervous system**: Dizziness (10%), paresthesia (8%), headache (7%), insomnia (7%), myasthenia (7%), anxiety (5%), chills (<5%), confusion (<5%), drowsiness (<5%), hypertonia (<5%), nervousness (<5%), neuropathy (<5%), depression (4%). **Dermatologic**: Skin rash (9%), diaphoresis (6%), alopecia (<5%), pruritus (<5%), xeroderma (<5%). Endocrine & metabolic: Weight loss (7%), hyperglycemia (6%), weight gain (5%), decreased libido (<5%), dehydration (<5%), gout (<5%), hypercholesterolemia (<5%). **Gastrointestinal**: Dyspepsia (7%), anorexia (6%), flatulence (6%), vomiting (6%), dysphagia (<5%), hernia (<5%), melena (<5%), periodontal abscess (<5%), xerostomia (<5%). **Genitourinary**: Urinary tract infection (9%), impotence (7%), difficulty in micturition (5%), urinary retention (5%), dysuria (<5%), urinary urgency (<5%), urinary incontinence (4%). **Hematologic & oncologic**: Gastrointestinal carcinoma (<5%), rectal hemorrhage (<5%), skin carcinoma (<5%) **Hepatic**: Increased liver enzymes (7%), increased serum alkaline phosphatase (5%). **Infection**: Herpes zoster (<5%), sepsis (<5%). **Neuromuscular & skeletal**: Ostealgia (9%), arthritis (5%), leg cramps (<5%), myalgia (<5%), neck pain (<5%), pathological fracture (4%). **Ophthalmic**: Cataract (<5%). Renal: Polyuria (6%), hydronephrosis (<5%), increased blood urea nitrogen (<5%), increased serum creatinine (<5%). **Respiratory**: Cough (8%), pharyngitis (8%), flu-like symptoms (7%), bronchitis (6%), asthma (<5%), epistaxis (<5%), sinusitis (<5%), pneumonia (4%), rhinitis (4%). **Miscellaneous**: Cyst (<5%), fever (<5%).
Monitoring Parameters	• Blood glucose. • Liver function tests. • Prostate-specific antigen (PSA). • Periodically monitor CBC, ECG, echocardiograms, serum testosterone, luteinizing hormone.

Drug Interactions	***Risk X: Avoid combination*** Aminolevulinic Acid (Systemic), Astemizole, Cisapride, Indium 111 Capromab Pendetide, Pimozide, Terfenadine. ***Risk D: Consider therapy modification*** Gallium Ga 68, PSMA-11 Lemborexant, Lomitapide, Lonafarnib, Piflufolastat F18 Sirolimus, Ubrogepant.
Pregnancy and Lactation	Bicalutamide is contraindicated in women, including pregnant and breastfeeding women. Teratogenic effects.
Administration	Oral Administration • Bicalutamide should be taken at the same time every day. • May be administered without regard to meals. • If a dose is missed, skip that dose and take the next dose at the usual time; do not take the missed dose and do not take a double dose. • Refer to manufacturer PIL for specific considerations.
Emetogenicity	Minimal
Warnings/ Precautions	***Concerns related to adverse effects:*** • Gynecomastia: Bicalutamide may cause gynecomastia or breast pain at higher (off-label) doses. • Hematologic: Anemia may occur with testosterone suppression; monitor CBC periodically as indicated. • Hepatotoxicity: Cases of death or hospitalization due to severe liver injury have been reported; discontinue if patients have jaundice or ALT is >2 × ULN. • Hypersensitivity: Angioneurotic edema and urticaria have been reported. • Interstitial lung disease: Promptly evaluate any worsening of respiratory symptoms (eg, dyspnea, cough and fever). ***Disease-related concerns:*** • Cardiovascular disease: Correct electrolytes prior to initiation and consider periodic electrolyte and ECG monitoring. • Decreased bone mineral density: In prolonged use of antiandrogen therapy. Evaluate risk carefully before initiating therapy. • Diabetes: When used in combination with LHRH agonists, a loss of glycemic control and a decrease in glucose tolerance have been reported in patients with diabetes. Monitor blood glucose. • Hepatic impairment: Use with caution in moderate to severe impairment; Consider periodic monitoring of liver function with prolonged therapy. ***Concurrent drug therapy issues:*** • Warfarin: Monitor PT/INR in patients on concomitant warfarin therapy and adjust warfarin dose as necessary. ***Other warnings/cautions:*** • Anti-androgen withdrawal syndrome: Discontinue use immediately if the disease worsens; Decreased prostate-specific antigen (PSA) levels and/or clinical improvement may be observed in some patients when antiandrogen therapy is

	held due to worsening of disease.
Storage and Light Sensitivity	• Store at room temperature of 20°C to 25°C. • No precautions needed for light protection. **N.B**. Refer to manufacturer PIL if there are specific considerations.
Patient Counselling Keys	• Risk of photosensitivity Patients should consider the use of sunscreen. • Monitor blood glucose. Hyperglycemia risk increases. • Avoid driving and doing other tasks or actions that call for you to be alert until you see how this drug affects you. • Wife of patient should use birth control to protect from pregnancy while taking this drug and for 130 days after last dose. • Bleeding has happened in people taking certain blood thinners like warfarin with this drug. Blood check routinely. • Missed doses should not be replaced if it is less than 12 hours until the next dose. • This drug is teratogenic.

3. Flutamide

Generic Name	Flutamide
Dosage Forms/ strengths	Tablets: 250mg
Route of Administration	Oral
Pharmacologic Category	Antineoplastic Agent, Antiandrogen ATC: L02BB01
Indications	**N.B.** Refer to literature and specific protocols for all indications. **Prostate cancer** that may be locally advanced or has metastasized (spread to other parts of the body). It is used in combination with a luteinizing hormone-releasing hormone agonist.
Dosage Regimen	**N.B.** Different doses and regimens may have been used; consult the literature for specific protocols. **Prostate cancer, locally advanced or metastatic:** Oral: 250 mg 3 times daily (every 8 hours) in combination with a luteinizing hormone-releasing hormone agonist.
Dosage Adjustment	**N.B.** Refer to the protocol used for specific dose modifications**.** **Dosing: Altered Kidney Function: Adult** No dosage adjustment is necessary in patients with chronic renal insufficiency. Use with caution. Dialysis: Flutamide and the active metabolite are not well dialyzed; Flutamide is not cleared by hemodialysis. Use with caution. **Dosage: Hepatic Impairment: Adult** Mild to moderate impairment: There are no dosage available. May not be needed. Severe impairment: Use is contraindicated if jaundice develops, or serum ALT or AST exceeds 2 to 3 x ULN.
Contra-indications	• Hypersensitivity to flutamide or any component of the formulation. • Severe hepatic impairment (evaluate baseline hepatic enzymes before treatment).
Adverse Drug Reactions	**>10%:** Endocrine & metabolic: Hot flash (46% to 61%), galactorrhea (9% to 42%), decreased libido (36%), increased lactate dehydrogenase (transient; mild) Gastrointestinal: Diarrhea (12% to 40%), vomiting (11% to 12%) Genitourinary: Impotence (33%), cystitis (16%), breast tenderness Hematologic & oncologic: Rectal hemorrhage (14%), flare tumor Hepatic: Increased serum AST (transient; mild) **1% to 10%:** Cardiovascular: Edema (4%), hypertension (1%) Central nervous system: Anxiety, confusion, depression, dizziness, drowsiness,

	headache, insomnia, nervousness Dermatologic: Skin rash (3% to 8%), ecchymoses, pruritus Endocrine & metabolic: Gynecomastia (9%) Gastrointestinal: Nausea (9%), proctitis (8%), gastric distress (4% to 6%), anorexia (4%), constipation, dyspepsia, increased appetite Genitourinary: Hematuria (7%) Hematologic & oncologic: Anemia (6%), leukopenia (3%), thrombocytopenia (1%) Infection: Herpes zoster Neuromuscular & Skeletal: Weakness (1%)
Monitoring Parameters	• CBC • Liver function test • Monitor prostate-specific antigen (PSA). • Consider monitoring methemoglobin levels in patients with hemoglobin M disease or with G6PD deficiency and in smokers. • Monitor adherence.
Drug Interactions	***Risk X: Avoid combination*** Indium 111 Capromab Pendetide. ***Risk D: Consider therapy modification*** Gallium Ga 68 PSMA-11, Flotufolastat F18, Piflufolastat F18.
Pregnancy and Lactation	Flutamide is not indicated for use in females.
Administration	**Oral:** May be administered without regard to food. Administer every 8 hours. **N.B.** Refer to manufacturer PIL for specific considerations.
Emetogenicity	Minimal
Warnings/ Precautions	***Concerns related to adverse effects:*** • Aniline toxicity: 4-nitro-3-fluoro-methylaniline is a flutamide metabolite. Patients with G6PD deficiency, hemoglobin M disease, and/or smokers are at risk of toxicities associated with aniline exposure, including methemoglobinemia, hemolytic anemia, and cholestatic jaundice; consider monitoring methemoglobin levels. • Gynecomastia: Gynecomastia may occur in patients receiving flutamide in combination with medical castration. • Hepatic failure: **[US Boxed Warning]: r**eports of hospitalization and death (rare) due to liver failure have been reported with flutamide. Evidence of hepatic injury, hepatic encephalopathy, and death related to acute hepatic failure. Hepatotoxicity was reversible after discontinuation in some cases. Closely monitor LFTs. Use is contraindicated in patients with severe hepatic impairment. ***Disease-related concerns:*** • Cardiovascular disease: Androgen-deprivation therapy may increase the risk for cardiovascular disease.

	Special populations: • Females: Flutamide is not indicated for use in females and should not be used in females, particularly for nonserious or non-life-threatening conditions.
Storage and Light Sensitivity	• Store from 15°C to 30°C. Dispense with a child-resistant closure in a tight, light-resistant container. • Protect from light. Dispense in a light-resistant container. **N.B** Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• If you have diarrhea with this drug, talk with your doctor. Decrease dairy products. • Increased sensitivity to ultraviolet (UV) light resulting in an exaggerated sunburn-like reaction accompanied by stinging sensations and urticaria. • May induce hepatotoxicity, abnormal appetite, Hair loss, cardiac disease (oedema). • Check CBC as you told. Anemia is induced. • Call doctor right away if Signs of methemoglobinemia appeared like a blue or gray color of the lips, nails, or skin; a heartbeat that does not feel normal; seizures; severe dizziness or passing out; severe headache; feeling very sleepy; feeling tired or weak; or shortness of breath.
Pharmaco-genomics	G6PD – Flutamide: Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency are more susceptible to developing methemoglobinemia during flutamide therapy. Monitor for signs and symptoms of methemoglobinemia when administering flutamide in patients with G6PD deficiency.

4. Fulvestrant

Generic Name	Fulvestrant
Dosage Form/ Strengths	• Solution for injection in Pre-filled Syringe: 250 mg/5ml • Solution for I.M Injection: 250 mg/5ml
Route of Administration	Intramuscular.
Pharmacologic Category	Antineoplastic Agent, Estrogen Receptor Antagonist. ATC Code: L02BA03.
Indications	**N.B.** *Refer to literature and specific protocols for all indications.* • **Monotherapy in breast cancer** - Treatment of hormone-receptor (HR) positive locally advanced or metastatic breast cancer in postmenopausal patients with disease progression following endocrine therapy. - Treatment of HR-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in postmenopausal patients not previously treated with endocrine therapy. • **Combination therapy in breast cancer** - Treatment of HR-positive, HER2-negative advanced or metastatic breast cancer (in combination with ribociclib) in postmenopausal patients as initial endocrine-based therapy or following disease progression on endocrine therapy. - Treatment of HR-positive, HER2-negative advanced or metastatic breast cancer (in combination with Palbociclib or abemaciclib) in females with disease progression following endocrine therapy.
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols.* • **Breast cancer, monotherapy:** **IM**: Initial: 500 mg on days 1, 15, and 29; Maintenance: 500 mg once monthly. • **Breast cancer, in combination** **IM**: Initial: 500 mg on days 1, 15, and 29; Maintenance: 500 mg once monthly. - The recommended dose of Ribociclib is oral 600 mg, once daily for 21 consecutive days followed by 7 days off treatment. - The recommended dose of Palbociclib is oral 125 mg once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. - The recommended dose of Abemaciclib is oral 150 mg, twice daily. **N.B.** For combination therapy regimens, with Palbociclib, Abemaciclib, or Ribociclib, pre/perimenopausal women should be treated with luteinizing

	hormone-releasing hormone (LHRH) agonists Prior to the start and throughout its duration according to current clinical practice standards.
Dosage Adjustment	**N.B.** *Refer to the protocol used for specific dose modifications.* • **Dosage in renal failure** - Mild to moderate renal impairment (creatinine clearance ≥30 ml/min): No dose adjustments are recommended. - Severe renal impairment: Not studied. Caution. • **Dosing: Hepatic Impairment:** - Mild hepatic impairment: No dosage adjustments necessary. Caution. - Moderate hepatic impairment: IM 250mg instead of 500mg. Caution. - Severe hepatic impairment: No data. Not studied.
Contra-indications	• Known hypersensitivity to Fulvestrant or any component of the formulation. • Pregnancy or lactation. • Severe hepatic impairment.
Adverse Drug Reactions	**>10%** **Endocrine and metabolic**: Decreased serum glucose (18%), hot flash (7% to 11%), increased gamma-glutamyl transferase (49%) **Gastrointestinal**: Abdominal pain (13% to 16%), constipation (5% to 12%), decreased appetite (8% to 13%), diarrhea (6% to 25%), nausea (10% to 28%), stomatitis (10% to 13%), vomiting (6% to 15%) **Hematologic and oncologic:** Anemia (4% to 40%; grade 3: ≤2%), lymphocytopenia (35%; grade 3: 2%) **Hepatic**: Increased liver enzymes (>15%), increased serum alanine aminotransferase (5% to 37%), increased serum aspartate aminotransferase (5% to 48%) **Infection**: Infection (25% to 31%) **Local**: Pain at the injection site (12%) **Nervous system**: Fatigue (8% to 32%), headache (8% to 15%) **Neuromuscular** & **skeletal**: Arthralgia (8% to 17%) **Respiratory**: Cough (5% to 15%), dyspnea (4% to 12%) **1% to 10%** **Cardiovascular**: Peripheral edema (7%) **Dermatologic**: Alopecia (2% to 6%), pruritus (6% to 7%), skin rash (4% to 7%) **Endocrine and metabolic**: Decreased serum albumin (8%), decreased serum phosphate (8%), weight loss (2%) **Gastrointestinal**: Anorexia (6%), dysgeusia (3%) **Hematologic & oncologic:** Leukopenia (≤5%; grade 3: 1%; grade 4: 1%), neutropenia (2%; grade 3: 1%; grade 4: <1%), thrombocytopenia (3%; grade 4: <1%) **Nervous system**: Dizziness (6% to 8%) **Neuromuscular and skeletal**: Asthenia (5% to 6%), back pain (8% to 9%), limb pain (6% to 7%), musculoskeletal pain (6%), myalgia (7%), ostealgia (9%)

	Miscellaneous: Fever (5% to 7%).
Monitoring Parameters	• Liver function tests. • Pregnancy testing is recommended within 7 days prior to Fulvestrant initiation. • Monitor for signs/symptoms of bleeding. • Screening for cardiovascular disease risk factors such as hypertension, diabetes, dyslipidemia, obesity, and smoking.
Drug Interactions	***Risk D: Consider therapy modification:*** Fluoroestradiol F18.
Pregnancy and Lactation	**Pregnancy**: Contraindicated. Fulvestrant Injection can cause fetal harm when administered to a pregnant woman. Women should use effective contraception during treatment with Fulvestrant and for 1 year after the last dose. The effects of Fulvestrant on fertility in humans has not been studied. **Lactation**: Contraindicated. Breast-feeding must be discontinued during treatment with Fulvestrant due to potential for serious adverse reactions.
Administration	**For IM administration only:** - Administer 500 mg dose as two 5 mL IM injections (one in each buttock [gluteal area]) slowly over 1 to 2 minutes per injection. - Because the underlying sciatic nerve is close to the dorsolateral injection site, care should be used when injecting Fulvestrant. **N.B.** Refer to manufacturer PIL for specific considerations.
Emetogenicity	Adults: Minimal (<10%).
Warnings/ Precautions	• **Blood Disorder:** As Fulvestrant is taken by intramuscular injection, it should be used cautiously when treating individuals with bleeding diatheses, thrombocytopenia, or those undergoing anticoagulant therapy. • **Thromboembolic Events:** - Thromboembolic events have been reported in Fulvestrant clinical trials and are frequently found in patients with advanced breast cancer. - When giving Fulvestrant to patients who are at risk, this should be considered. • **Injection Reactions:** With Fulvestrant injection, injection site-related symptoms such as sciatica, neuralgia, neuropathic pain, and peripheral neuropathy have been documented. • **Combination with alcohols:** Each injection contains 500 mg of alcohol (ethanol) equivalent to 100 mg/ml (10% w/v) ethanol. Co-administration with medicines containing e.g. propylene glycol or ethanol may lead to accumulation of ethanol and induce adverse effects. It contains also benzyl alcohol. Caution in hepatic disease and epileptic patients.

	• **Bone effect:** A potential risk for osteoporosis. No long-term data on Fulvestrant bone effects. • **Interference with estradiol antibody assays** Due to the structural similarity of Fulvestrant and Estradiol, Fulvestrant may interfere with antibody based-estradiol assays and may result in falsely increased levels of Estradiol.
Storage and Light Sensitivity	Store Fulvestrant refrigerated between 2°C to 8°C. Protect from light. **N.B.** Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• Follow your doctor's advised treatment schedule. Your medicine will still work even if the dose is moved up a few days from what is originally intended. • This drug may affect certain lab tests. Tell all of your health care providers and lab workers that you take this drug. • This drug may cause harm to an unborn baby. Contraception methods should be used for at least 1 year after the last dose. Fluvestrant is not recommended during lactation.

B. Aromatase Inhibitors

1. Anastrazole

Generic Name	Anastrozole
Dosage Forms/ Strengths	Tablets 1 mg
Route of Administration	Oral
Pharmacologic Category	Antineoplastic Agent, Aromatase Inhibitor ATC: L02BG03
Indications	**N.B.** *Refer to literature and specific protocols for all indications*. **Breast cancer in postmenopausal women:** • Locally advanced or metastatic breast cancer hormone receptor-positive. • Adjuvant treatment of hormone receptor-positive early breast cancer. • Treatment of advanced breast cancer with disease progression following tamoxifen therapy
Dosage Regimen	**N.B.** *Different doses and regimens may have been used; consult the literature for specific protocols.* **Oral:** 1 mg once daily; continue until tumor progression to complete a total of 5 to 10 years of adjuvant endocrine therapy.
Dosage Adjustment	**N.B.** *Refer to protocol used for specific dose modifications*. **Dosing: Altered Kidney Function: Adult** No dosage adjustment necessary. Caution if eGFR less than 30 mL/minute/1.73m^2 **Dosing: Hepatic Impairment: Adult** Mild to moderate impairment or stable hepatic cirrhosis: No dosage adjustment necessary. Severe impairment: not recommended.
Contra-indications	• Hypersensitivity to Anastrozole or any component of the formulation • Premenopausal women
Adverse Drug Reactions	**Adverse Reactions Significant Considerations** • Bone mineral density loss/increased fracture risk: Decreased bone mineral density from baseline ~7% loss after 5 years have been reported • Ischemic cardiovascular events: in patients with preexisting cardiovascular disease and long duration (more than 3 years). • Musculoskeletal effects: new onset or exacerbation of existing arthralgia, joint stiffness, and/or ostealgia. **>10%** **Cardiovascular**: Angina pectoris (2%; 12% in patients with preexisting ischemic heart disease) (See Table 1), hypertension (5% to 13%), ischemic heart disease (4%; increased incidence of ischemic cardiovascular events seen in patients

with preexisting ischemic heart disease: 17%) (See Table 2), vasodilation (25% to 36%).
Dermatologic: Skin rash (6% to 11%).
Endocrine & metabolic: Hot flash (12% to 36%).
Gastrointestinal: Gastrointestinal distress (29% to 34%), nausea (11% to 19%), vomiting (≤13%).
Nervous system: Depression (5% to 13%), fatigue (≤19%), headache (9% to 13%), mood disorder (19%), pain (11% to 17%).
Neuromuscular & skeletal: Arthralgia (15%), arthritis (17%), asthenia (≤19%), back pain (10% to 12%), ostealgia (7% to 11%), osteoporosis (11%).
Respiratory: Increased cough (8% to 11%), pharyngitis (6% to 14%).

1% to 10%

Cardiovascular: Acute myocardial infarction (1%), cerebral ischemia (2%), chest pain (5% to 7%), deep vein thrombosis (2%), edema (7%), peripheral edema (5% to 10%), thromboembolic disease (3%), thrombophlebitis (2% to 5%), venous thrombosis (3%).
Dermatologic: Alopecia (2% to 5%), diaphoresis (2% to 5%), pruritus (2% to 5%).
Endocrine & metabolic: Hypercholesterolemia (9%), increased gamma-glutamyl transferase (2% to 5%), weight gain (2% to 9%), weight loss (2% to 5%).
Gastrointestinal: Abdominal pain (7% to 9%), anorexia (5% to 7%), constipation (7% to 9%), diarrhea (8% to 9%), dyspepsia (7%), gastrointestinal disease (7%), xerostomia (4% to 6%).
Genitourinary: Leukorrhea (2% to 3%), mastalgia (8%), pelvic pain (5%), urinary tract infection (8%), vaginal discharge (4%), vaginal dryness (2%), vaginal hemorrhage (1% to 5%), vaginitis (4%), vulvovaginitis (6%).
Hematologic & oncologic: Anemia (4%), leukopenia (2% to 5%), lymphedema (10%), neoplasm (5%), tumor flare (3%).
Hepatic: Increased serum alanine aminotransferase (2% to 5%), increased serum alkaline phosphatase (2% to 5%), increased serum aminotransferase (2% to 5%).
Infection: Infection (9%).
Nervous system: Anxiety (6%), carpal tunnel syndrome (3%), confusion (2% to 5%), dizziness (6% to 8%), drowsiness (2% to 5%), hypertonia (3%), insomnia (6% to 10%), lethargy (1%), malaise (2% to 5%), nervousness (2% to 5%), paresthesia (5% to 7%).
Neuromuscular & skeletal: Arthropathy (6% to 7%), bone fracture (10%), myalgia (6%), neck pain (2% to 5%), pathological fracture (2% to 5%).
Ophthalmic: Cataract (6%).
Respiratory: Bronchitis (5%), dyspnea (8% to 10%), flu-like symptoms (6% to 7%), rhinitis (2% to 5%), sinusitis (6%).
Miscellaneous: Accidental injury (10%), cyst (5%), fever (2% to 5%).

Monitoring Parameters	• Bone mineral density at baseline and periodically thereafter. • Total cholesterol and LDL. • Pregnancy test (prior to treatment in females of reproductive potential). • Monitor adherence.
Drug Interactions	***Risk X: Avoid combination*** Estrogen Derivatives, Tamoxifen.
Pregnancy and Lactation	**Pregnancy:** Anastrozole may cause fetal harm if exposure occurs during pregnancy. May impair fertility in females of reproductive potential. **Lactation**: Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended during therapy or for 2 weeks after the last Anastrozole dose.
Administration	**Oral:** May be administered with or without food. **N.B**. Refer to manufacturer PIL for specific considerations.
Emetogenicity	Minimal
Warnings/ Precautions	***Disease-related concerns:*** • Hepatic impairment: Plasma concentrations in patients with stable hepatic cirrhosis were within the range of concentrations seen in normal subjects across all clinical trials. Has not been studied in patients with severe hepatic impairment. ***Special populations:*** • Premenopausal females: Aromatase inhibitors (including anastrozole) should not be used as monotherapy in premenopausal females with breast cancer. Premenopausal females with metastatic breast cancer should be offered ovarian suppression or ablation along with hormonal therapy
Storage and Light Sensitivity	Store at 20°C to 25°C. No precautions needed for light protection. **N.B.** Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• Have your scheduled CBC and bone density testing. • This drug lowers the estrogen in your body, which may cause weak bones which increase liability of fractures. Consider daily oral supplements of calcium and vitamin D for the duration of the therapy. • May cause hypercholesterolemia. • This drug is teratogenic and carcinogenic.

2. Exemestane

Generic Name	Exemestane
Dosage Form/ Strengths	Tablets: 25mg
Route of Administration	Oral
Pharmacologic Category	Antineoplastic Agent, Aromatase Inhibitor ATC:L02BG06
Indications	**N.B.** Refer to literature and specific protocols for all indications. **Breast cancer (**in postmenopausal patients)**:** • Adjuvant treatment of estrogen receptor–positive early breast cancer in postmenopausal patients who have received 2 to 3 years of tamoxifen (for completion of a total of 5 consecutive years of adjuvant hormonal therapy). • Treatment of advanced breast cancer in postmenopausal patients after tamoxifen therapy fail. May be used in combinations.
Dosage Regimen	**N.B.** Different doses and regimens may have been used; consult the literature for specific protocols. **Breast cancer, adjuvant therapy** *Adjuvant treatment following 2 to 3 years of tamoxifen:* Postmenopausal patients: **Oral:** 25 mg once daily (following 2 to 3 years of tamoxifen therapy) for a total duration of 5 years of endocrine therapy (in the absence of recurrence or contralateral breast cancer). *Breast cancer, advanced***:** Postmenopausal patients: **Oral:** 25 mg once daily; continue until tumor progression.
Dosage Adjustment	**N.B.** Refer to protocol used for specific dose modifications. **Dosing: Altered Kidney Function: Adult** No adjustment necessary. Use with caution. **Dosage: Hepatic Impairment: Adult** No adjustment necessary. Use with caution. **Dosing: Adjustment for Toxicity: Adult** Decreased bone mineral density: Manage bone density loss as clinically indicated. Vitamin D deficiency: Supplement as clinically indicated.
Contra-indications	Known hypersensitivity to exemestane or any component of the formulation.
Adverse Drug Reactions	**>10%** **Cardiovascular**: Hypertension (5% to 15%). **Dermatologic**: Alopecia (15%), hyperhidrosis (4% to 12%). **Endocrine & metabolic**: Hot flash (13% to 33%). **Gastrointestinal**: Nausea (9% to 18%).

	Hematologic & oncologic: Lymphocytopenia (grades 3/4: 20%). **Hepatic**: Increased serum alkaline phosphatase (14% to 15%). **Nervous system**: Depression (6% to 13%), fatigue (8% to 22%), headache (7% to 13%), insomnia (11% to 12%), pain (13%). **Neuromuscular & skeletal**: Arthralgia (15%). **1% to 10%** **Cardiovascular**: Acute myocardial infarction (≤2%), angina pectoris (≤2%), chest pain (2% to 5%), edema (≤7%), ischemic heart disease (≤2%), lower extremity edema (≤ 7%), peripheral edema (≤7%). **Dermatologic**: Dermatitis (8%), pruritus (2% to 5%), skin rash (2% to 5%) **Endocrine & metabolic**: Increased gamma-glutamyl transferase (grades 3/4: 3%), weight gain (8%). **Gastrointestinal**: Abdominal pain (6%), anorexia (6%), constipation (5%), diarrhea (4% to 10%), dyspepsia (2% to 5%), increased appetite (3%), vomiting (7%). **Genitourinary**: Urinary tract infection (2% to 5%). **Hematologic & oncologic**: Lymphedema (2% to 5%). **Hepatic**: Increased serum bilirubin (5% to 7%). **Infection**: Infection (2% to 5%). **Nervous system**: Anxiety (10%), carpal tunnel syndrome (2%), confusion (2% to 5%), dizziness (8% to 10%), hypoesthesia (2% to 5%), paresthesia (3%), tumor pain (8%) **Neuromuscular & skeletal**: Asthenia (6%), back pain (9%), limb pain (9%), muscle cramps (2%), myalgia (6%), osteoarthritis (6%), osteoporosis (5%), pathological fracture (4%), skeletal pain (2% to 5%). **Ophthalmic**: Visual disturbance (5%). **Renal**: Increased serum creatinine (6%). **Respiratory**: Bronchitis (2% to 5%), cough (6%), dyspnea (10%), flu-like symptoms (6%), pharyngitis (2% to 5%), rhinitis (2% to 5%), sinusitis (2% to 5%), upper respiratory tract infection (2% to 5%). **Miscellaneous**: Fever (5%).
Monitoring Parameters	• Assess bone mineral density at baseline in patients with, or at risk for osteoporosis; monitor for bone density loss during exemestane therapy. • Pregnancy testing • Serum 25(OH) hydroxyvitamin D concentrations
Drug Interactions	***Risk X: Avoid combination*** Estrogen Derivatives, St John's Wort. ***Risk D: Consider therapy modification*** Barbiturates (phenobarbital), Carbamazepine, Phenytoin, Rifampicin.
Pregnancy and Lactation	**Pregnancy**: Exemestane can cause fetal harm if administered to a pregnant patient. Use effective contraception while treatment and for 1 month after the last dose. Male and female fertility may be impaired by treatment with Exemestane.

	Lactation: Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended during treatment and for 1 month after the final exemestane dose.
Administration	• Oral: Administer after a meal. • **N.B**. Refer to manufacturer PIL for specific considerations.
Emetogenicity	Minimal
Warnings/ Precautions	***Concerns related to adverse effects:*** • Decreased bone mineral density: Due to decreased circulating estrogen levels, exemestane is associated with a reduction in bone mineral density over time. Decreases (from baseline) in lumbar spine and femoral neck density have been observed (when compared to tamoxifen or placebo in studies where concomitant use of bisphosphonates, calcium and vitamin D were not allowed). • Lymphopenia: Grade 3 or 4 lymphopenia has been observed with exemestane, although most patients had pre-existing lower grade lymphopenia; Some patients improved or recovered while continuing exemestane. Lymphopenia did not result in a significant increase in viral infections, and no opportunistic infections were observed. • Lab parameters: Elevations of AST, ALT, alkaline phosphatase, and gamma glutamyl transferase >5 times ULN have been observed (rarely) in patients with advanced breast cancer; may be attributable to underlying liver and/or bone metastases. In patients with early breast cancer, elevations of bilirubin, alkaline phosphatase, and serum creatinine were more common with exemestane treatment than with tamoxifen or placebo. ***Concurrent drug therapy issues:*** • Estrogen-containing drugs: Exemestane should not be administered concurrently with estrogen-containing medications.
Storage and Light Sensitivity	• Store from 15°C to 30°C. • No precautions needed for light protection. **N.B**. Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• Consider daily oral supplements of calcium and vitamin D for the duration of the therapy. • A pregnancy test will be done before you start this drug to show that you are Not pregnant due to possible harm for unborn baby. This drug may affect fertility. • Check blood pressure as this drug may cause high blood pressure.

3. Letrozole

Generic Name	Letrozole
Dosage Forms/ Strengths	2.5 mg tablets
Route of Administration	Oral
Pharmacologic Category	Antineoplastic agent, aromatase inhibitor. ATC: L02BG04
Indications	**N.B.** *Refer to literature and specific protocols for all indications.* **Breast cancer in postmenopausal patients** - Adjuvant treatment of women with hormone receptor positive (HR+) early breast cancer. - Extended adjuvant treatment of hormone-dependent early breast cancer in women who have received prior standard adjuvant tamoxifen therapy for 5 years. - First-line treatment in women with hormone-dependent advanced breast cancer. - Advanced breast cancer in women with natural or artificially induced postmenopausal status after relapse or disease progression, who have previously been treated with anti-oestrogens. - Efficacy has not been demonstrated in patients with hormone receptor negative breast cancer.
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols***.** **Adult Dosing:** Oral tablets without regarding meals. Recommended dose: 2.5.mg once daily.
Dosage Adjustment	**N.B.** *Refer to protocol used for specific dose modifications.* **Dosage in renal failure** Creatinine clearance is ≥10 mL/min.: No dosage adjustment necessary. Severe renal impairment: Not recommended due to insufficient data. **Dosage in hepatic failure** No dosage adjustment necessary. Severe impairment (Child-Pugh class C) and cirrhosis: 2.5 mg every other day. Insuffecient data. **Dosing: Adjustment for Toxicity: Adult** Hyperlipidemia: May require antihyperlipidemic medication
Contra-indications	• Known hypersensitivity to letrozole or any component of the formulation. • Premenopausal status. • Pregnancy or lactation.

Adverse Drug Reactions	**Bone mineral density loss/increased fracture risk:** Letrozole is associated with a decreased bone mineral density (BMD), in postmenopausal females, an increased risk of osteoporosis and bone fracture should be considered with administering treatment. **Ischemic heart disease**: (Angina pectoris and acute myocardial infarction (MI) have occurred.) **Musculoskeletal effects:** (including new onset or exacerbation of existing arthralgia, joint stiffness, and/or ostealgia) **>10%** **Cardiovascular**: Edema (7% to 18%), flushing (50%). **Dermatologic**: Diaphoresis (24%), night sweats (15%). **Endocrine & metabolic**: Hot flash (19% to 34%), hypercholesterolemia (52%), weight gain (13%). **Gastrointestinal**: Nausea (9% to 17%). **Nervous system**: Dizziness (3% to 14%), fatigue (10% to 13%). **Neuromuscular & skeletal**: Arthralgia (≤25%), arthritis (≤25%), asthenia (6% to 34%), back pain (5% to 18%), bone fracture (10% to 15%), ostealgia (5% to 22%), osteoporosis (5% to 15%). **Respiratory**: Cough (13%), dyspnea (6% to 18%). **1% to 10%** **Cardiovascular**: Acute myocardial infarction (1% to 2%), angina pectoris (1%), cardiac failure (1% to 2%), cerebrovascular accident (≤3%), chest pain (6% to 8%), chest wall pain (6%), hemorrhagic stroke (≤2%), hypertension (6% to 8%), peripheral edema (5%), thromboembolism (≤3%; including portal vein thrombosis, pulmonary embolism, thrombophlebitis, venous thrombosis), thrombotic stroke (≤2%), transient ischemic attacks (≤3%). **Dermatologic**: Alopecia (3%). **Endocrine & metabolic**: Weight loss (6% to 7%). **Gastrointestinal**: Anorexia (≤4%), constipation (2% to 10%), diarrhea (8%), vomiting (3% to 7%). **Genitourinary**: Mastalgia (2% to 7%), urinary tract infection (6%), vaginal hemorrhage (5%), vaginal irritation (5%). **Hematologic & oncologic**: Lymphedema (7%; post-mastectomy), second primary malignant neoplasm (2% to 5%). **Infection**: Infection (7%), influenza (6%). **Nervous system**: Depression (5%), headache (4% to 8%), hemiparesis (≤2%), insomnia (6% to 7%), lethargy (<10%), malaise (<10%), pain (5%). **Neuromuscular & skeletal**: Limb pain (4% to 10%), myalgia (7% to 9%), osteopenia (4%). **Ophthalmic**: Cataract (2%). **Renal**: Renal disease (5%).
Monitoring	• Hormone receptor status.

Parameters	• Liver function test (at baseline). • Monitoring cholesterol level. • Bone mineral density.
Drug Interactions	***Risk X: Avoid combination*** Tamoxifen: it decreases the serum level of Letrozole which decreases its effect.
Pregnancy and Lactation	**Pregnancy:** Contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. **Lactation:** is not recommended due to the potential risk.
Administration	**Administration**: Oral: Administer without regard to meals. Calcium and vitamin D supplementation are recommended. N.B. Refer to manufacturer PIL for specific considerations.
Emetogenicity	Emetogenic potential: non-emetogenic.
Warnings/ Precautions	**Bone Effects:** Consideration should be given to monitoring bone mineral density. **Cholesterol:** Consideration should be given to monitoring serum cholesterol. Amongst patients who had baseline values of total serum cholesterol within the normal range, increase in total serum cholesterol higher than 1.5 times the ULN were observed in 5.4% of the patients in the letrozole arm, compared with 1.1% in the tamoxifen arm. **CNS depression: eg. Fatigue and Dizziness:** Caution is advised when driving or using machinery until it is known how the patient reacts to Letrozole use. **Tendonitis and tendon ruptures** (rare) may occur. Close monitoring of the patients and appropriate measures (e.g. immobilisation) must be initiated for the affected tendon.
Storage and Light Sensitivity	Store between 20°C -25°C. No light sensitivity. N.B. Refer to manufacturer PIL for specific considerations
Patient Counselling Keys	• Take letrozole exactly as directed by a doctor. Follow your lab' schedule as instructed by your doctor. • Letrozole may be taken with food or on an empty stomach. • Other drugs such as Tamoxifen may interact with letrozole. • Avoid taking estrogen replacement therapy such as conjugated estrogens. • Consideration should be given to monitoring bone mineral density, and cholesterol levels. • Tell your doctor if you have high cholesterol, osteoporosis (a condition in

which the bones are fragile and break easily), or liver disease.
- You should know that letrozole may make you drowsy. Do not drive a car or operate machinery until you know how this medication affects you.

C. Estrogen Receptor Blocker

1. Tamoxifen

Generic Name	Tamoxifen
Dosage Forms/ Strengths	Tablets: 10 mg and 20 mg.
Route of Administration	Oral
Pharmacologic Category	Antineoplastic Agent, Estrogen Receptor Antagonist; Selective Estrogen Receptor Modulator (SERM). ATC CODE: L02BA01
Indications	**N.B.** *Refer to literature and specific protocols for all indications.* • Treatment of breast cancer. • Ductal Carcinoma in Situ (the earliest form of breast cancer) • Stimulate ovulation in anovulatory infertility. • Primary prevention of breast cancer in women at moderate or high risk in women older than 30 years of age.
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols.* • **Treatment of breast cancer.** 20 mg Daily once per day. • **Ductal Carcinoma in Situ, prevention of breast cancer:** 20 mg once daily for 5 years. • **Stimulate ovulation in anovulatory infertility.** 20mg daily. If no signs of ovulation, then the subsequent course of treatment may be 40mg then 80mg daily.
Dosage Adjustment	**N.B.** *Refer to protocol used for specific dose modifications.* **Dosage in Altered Kidney Function** No dose adjustments are required. **Dosage in Hepatic Impairment** No dose adjustment recommendations are available.
Contra-indications	• Hypersensitivity (e.g. angioedema, serious skin reactions) to Tamoxifen or any component of the formulation. • Pregnancy. • Patients with concomitant warfarin therapy (for prevention indications). • Patients have a history of deep vein thrombosis or pulmonary embolus (for infertility or prevention indications).
Adverse Drug Reactions	**Hot flushes** **Hepatotoxicity** **Severe cutaneous adverse reactions** **Visual disturbances**

	Thromboembolic Events **Secondary malignancies (endometrial carcinoma)** **>10%** Fluid retention, Hot flushes, Nausea, Skin Rash, Vaginal bleeding, Vaginal discharge, Depression. **1% to 10%** Uterine Fibroids, Anemia, Hypersensitivity reactions, Ischemic cerebrovascular events, Headache, Light headedness, Sensory disturbances (including paresthesia and dysgeusia), Cataracts, Retinopathy, Thromboembolic events (including deep vein thrombosis, microvascular thrombosis and pulmonary embolism), Vomiting, Diarrhea, Constipation, Changes in liver enzymes, Fatty liver, Alopecia.
Monitoring Parameters	• CBC with differential. • Liver function test. • Lipid profile. • Serum calcium level (Tamoxifen causes hypercalcemia). • Monitor closely for skin reactions. • Pregnancy testing
Drug Interactions	***Risk X: Avoid combination*** Aromatase Inhibitors (Anastrozole, Letrozole), Strong CYP3A4 Inducers (e.g. Barbiturates, (phenobarbital), Carbamazepine, Phenytoin, Rifampicin), Ospemifene, Vitamin K Antagonists (e.g. warfarin). ***Risk D: Consider therapy modification*** Moderate or strong CYP2D6 Inhibitors (e.g. Paroxetine), Fluoroestradiol F18, Ribociclib. **Notes:** • **Warfarin:** Avoid combination as marked increase in anticoagulant effect may occur when Tamoxifen is used in combination with warfarin. • **Grapefruit juice and Tamoxifen:** Grapefruit juice inhibits the CYP 3A4 metabolism of Tamoxifen in the intestine and may increase tamoxifen plasma levels.
Pregnancy and Lactation	**Pregnancy:** Contraindicated. There is positive evidence of animal fetal risk. Women should avoid getting pregnancy during Tamoxifen treatment and for 9 months after the last dose. **Lactation**: Not recommended due to the potential secretion into breast milk. Tamoxifen may inhibit lactation.
Administration	**Hazardous agent (NIOSH 2016 [group 1]):** Known to be human carcinogen and teratogenic. **Oral**: Patients may take the drug without regard to food, at the same time each day. **N.B**. Refer to manufacturer PIL for specific considerations.
Emetogenicity	None

Warnings/ Precautions	**Hepatotoxicity:** usually consists of transient asymptomatic elevation of hepatic enzymes. However, more serious liver abnormalities, including fatty liver, cholestasis, and hepatitis, have occurred infrequently; rarely fatalities have been reported. **Secondary malignancies**: An increased incidence of uterine malignancies (endometrial adenocarcinoma and uterine sarcoma) has been reported in association with Tamoxifen treatment. The underlying mechanism is unknown but may be related to the estrogen-like effect of tamoxifen. Other risk factors include higher age, obesity, diabetes mellitus and polycystic ovary syndrome. There is also the general risk for endometrial cancer with increasing age. **Hereditary angioedema**: Tamoxifen may induce or exacerbate symptoms of angioedema. **Thromboembolic Events:** Tamoxifen treatment has increased risk of thromboembolic events by 2-3-fold. For treatment of breast cancer, consider the risks and benefits of tamoxifen in women with a history of thromboembolic events. Advise patients to seek medical attention immediately if signs of a thromboembolic event occur. **Embryo-Fetal Toxicity:** Tamoxifen can cause fetal harm when administered to a pregnant woman. **Hematologic Effects:** Leukopenia has been observed, sometimes in association with anemia and/or thrombocytopenia which may be severe cases. Perform periodic complete blood counts, including platelet counts. **Lipid profile:** Tamoxifen may lead to reductions in levels of blood total cholesterol and low-density lipoproteins in postmenopausal women by 10-20%. **Hypercalcemia in Patients with Metastatic Breast Cancer:** Tamoxifen does not adversely affect bone mineral density in postmenopausal women. A transient bone pain, local disease flare (increase in size of preexisting lesions, swelling and redness) and/or hypercalcemia may occur at the initiation of therapy in patients with metastatic disease. Patients with increased bone pain may require additional analgesics. If the hypercalcemia is severe, discontinue tamoxifen. **Severe cutaneous adverse reactions** including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be fatal. Discontinue treatment if symptoms appeared, and an alternative treatment is considered. If the patient has developed a serious reaction, treatment with tamoxifen must not be restarted at any other time. **Visual disturbances**: Corneal changes, retinopathy, and cataracts have been reported. May occur at any time after Tamoxifen initiation and may last after tamoxifen discontinuation. **T4 elevations** were reported rarely. These elevations were not accompanied by clinical hyperthyroidism.
Storage and Light Sensitivity	• Tablets: Store at 20°C to 25°C. • Protect from light. Avoid excessive heat.

	N.B. Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• Tell your doctor about any drugs you take. Check with your doctor or pharmacist before you start taking any new drugs. • This drug may cause dermal reactions or thromboembolic events e.g. a blood clot like chest pain or pressure; coughing up blood; shortness of breath. Call your doctor immediately. • This drug may cause signs of high calcium levels like weakness, headache, constipation, or bone pain. Talk with the doctor. • This drug may stop you from having a period (menstrual bleeding) for some time.
Pharmaco-genomics	**CYP2D6:** This gene is responsible for the conversion of Tamoxifen to the active metabolite endoxifen. • **Poor CYP2D6 metabolizers** may experience reduced effect of Tamoxifen due to reduction in plasma level of an active Tamoxifen metabolite. Avoid coadministration of strong CYP2D6 inhibitors (e.g. Paroxetine, Fluoxetine, Quinidine, Cinacalcet or Bupropion), and consider monitoring endoxifen concentrations.

D. Gonadotropin-Releasing Hormone Agonist

1. Goserelin

Generic Name	Goserelin
Dosage Form/ Strengths	Prefilled syringe for S.C injection (Depot Implant): 10.8 mg Prefilled syringe for S.C injection (Implant): 3.6 mg Implant with applicator: 3.6 mg.
Route of Administration	Subcutaneous.
Pharmacologic Category	Antineoplastic Agent, Gonadotropin-Releasing Hormone Agonist. **ATC Code:** L02AE03.
Indications	**N.B.** *Refer to literature and specific protocols for all indications.* • **Prostate cancer** - Metastatic prostate cancer. - Locally advanced prostate cancer, as an alternative to surgical castration. - Adjuvant treatment to radiotherapy or neo-adjuvant treatment before radiotherapy in patients with high-risk localized or locally advanced prostate cancer. - As adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression. - Management of locally confined carcinoma (in combination with an antiandrogen [e.g., Flutamide]). • **Breast cancer** - Advanced breast cancer in pre and perimenopausal women suitable for hormonal manipulation. - Early breast cancer in pre and perimenopausal women with positive estrogen receptor (ER). • **Endometriosis (3.6 mg only)** - As an endometrial-thinning agent before endometrial ablation or resection. - In managing endometriosis to alleviate symptoms, including pain, and reduce the size and number of endometrial lesions. • **Uterine fibroids (3.6 mg only)**: Prior to surgery, in conjunction with iron therapy in the hematological improvement of anemic patients with fibroids. Taken for up to three months before surgery. • **Assisted reproduction (3.6 mg only)**: Pituitary downregulation in preparation for superovulation.
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols.* **Adult dosing** **SC**: 3.6 mg injected into the anterior abdominal wall, every 4 weeks.

	SC: 10.8 mg injected into the anterior abdominal wall every 12 weeks. **Notes** **Breast Cancer:** intended for long term use unless clinically inappropriate**.** Treatment must be initiated at least 6-8 weeks before starting aromatase inhibitor treatment and administered without interruption throughout aromatase inhibitor treatment. **Endometriosis**: Management of endometriosis has been limited to women 18 years of age and older treated for 6 months. Repeated courses should not be given due to concern about loss of bone mineral density. Addition of hormone replacement therapy (a daily estrogenic agent and a progestogenic agent) has been shown to reduce bone mineral density loss and vasomotor symptoms. **Prostate:** When taken with Flutamide, Treatment with Goserelin should start 8 weeks prior to initiating radiation therapy and continue during radiation therapy. **Pediatric dosing** Not indicated for use in children.
Dosage Adjustment	**N.B.** *Refer to protocol used for specific dose modifications.* **Altered Kidney function** No dosage adjustment is necessary. **Hepatic Impairment** No dosage adjustment is necessary.
Contra-indications	Hypersensitivity to Goserelin or any component of the formulation. Pregnancy.
Adverse Drug Reactions	**>10%** **Cardiovascular**: Peripheral edema (females: 21%; males: 1% to 5%), vasodilation (females: 57%). **Dermatologic**: Acne vulgaris (females: 42%), diaphoresis (females: 16% to 45%; males: 6%), seborrhea (females: 26%). **Endocrine & metabolic**: Decreased libido (females: 48% to 61%), hot flash (females: 70% to 96%; males: 60% to 62%), increased libido (females: 12%). **Gastrointestinal**: Abdominal pain (1% to 11%), nausea (5% to 11%). **Genitourinary**: Breast atrophy (females: 33%), breast hypertrophy (females: 18%), decrease in erectile frequency (18%), dyspareunia (females: 14%), genitourinary signs and symptoms (lower; males: 13%), pelvic symptoms (females: 18%), sexual disorder (males: 21%), vaginitis (75%). **Hematologic & oncologic**: Tumor flare. **Infection**: Infection (females: 13%). **Nervous system**: Asthenia (5% to 11%), depression (females: 54%; males: 1% to 5%), emotional lability (females: 60%), headache (females: 32% to 75%; males: 1% to 5%), insomnia (5% to 11%), pain (8% to 17%). **Neuromuscular & skeletal**: Decreased bone mineral density. **1% to 10%** **Cardiovascular**: Acute myocardial infarction (males: 1% to 5%), angina pectoris (males: 1% to 5%), cardiac arrhythmia (males: 1% to 5%), chest pain (1% to 5%),

edema (5% to 7%), heart failure (males: 5%), hypertension (6%), palpitations (females: 1% to 5%), peripheral vascular disease (males: 1% to 5%), pulmonary embolism (males: 1% to 5%), tachycardia (females: 1% to 5%), varicose veins (males: 1% to 5%).
Dermatologic: Alopecia (females: 1% to 5%), ecchymoses (females: 1% to 5%), hair disease (females: 4%), pruritus (2%), skin discoloration (females: 1% to 5%), skin rash (6%), xeroderma (females: 1% to 5%).
Endocrine & metabolic: Diabetes mellitus (males: 1% to 5%), gynecomastia (males: 8%), hirsutism (females: 7%), hyperglycemia (males: 1% to 5%), weight gain (3%).
Gastrointestinal: Anorexia (5%), constipation (1% to 5%), diarrhea (1% to 5%), dyspepsia (females: 1% to 5%), flatulence (females: 1% to 5%), gastric ulcer (males: 1% to 5%), hematemesis (males: 1% to 5%), increased appetite (females: 2%), vomiting (4%), xerostomia (females: 1% to 5%).
Genitourinary: Bladder neoplasm (males: 1% to 5%), breast swelling (males: 1% to 5%), breast tenderness (males: 1% to 5%), dysmenorrhea (1% to 5%), hematuria (males: 1% to 5%), impotence (males: 1% to 5%), mastalgia (7%), pelvic pain (6% to 9%), urinary frequency (1% to 5%), urinary incontinence (males: 1% to 5%), urinary retention (males: 1% to 5%), urinary tract abnormality (males: 1% to 5%), urinary tract infection (1% to 5%), urinary tract obstruction (males: 1% to 5%), urination disorder (males: 1% to 5%), uterine hemorrhage (6%), vaginal hemorrhage (1% to 5%), vulvovaginitis (5%).
Hematologic & oncologic: Anemia (males: 1- 5%), hemorrhage (females: 1-5%).
Hypersensitivity: Hypersensitivity reaction (females: 1% to 5%).
Infection: Herpes simplex infection (males: 1% to 5%), sepsis (males: 1% to 5%)
Local: Application-site reaction (females: 6%).
Nervous system: Abnormality in thinking (females: 1% to 5%), anxiety (1% to 5%), cerebral ischemia (males: 1% to 5%), cerebrovascular accident (males: 1% to 5%), chills (males: 1% to 5%), dizziness (5% to 6%), drowsiness (females: 1% to 5%), fatigue (females: ≤5%), hypertonia (females: 1%), lethargy (≤8%), malaise (females: ≤5%), migraine (females: 7%), nervousness (females: 3% to 5%), paresthesia (1% to 5%), voice disorder (females: 3%).
Neuromuscular & skeletal: Arthralgia (females: 1% to 5%), arthropathy (females: 1% to 5%), back pain (4% to 7%), gout (males: 1% to 5%), lower limb cramp (females: 2%), myalgia (females: 3%), ostealgia (males: 6%).
Ophthalmic: Amblyopia (females: 1%- 5%), dry eye syndrome (females: 1%- 5%).
Renal: Renal insufficiency (males: 1% to 5%).
Respiratory: Bronchitis (females: 1% to 5%), chronic obstructive pulmonary disease (males: 5%), cough (1% to 5%), dyspnea (males: 1% to 5%), epistaxis (females: 1% to 5%), flu-like symptoms (5%), pharyngitis (females: 5%), pneumonia (males: 1% to 5%), rhinitis (females: 1% to 5%), sinusitis (females: 1% to 5%), upper respiratory tract infection (males: 7%).
Miscellaneous: Fever (1% to 5%).

Monitoring Parameters	• Blood glucose and HbA • Bone mineral density. • Electrocardiograms and electrolytes. • Serum calcium. • Lipid profile. • Monitor for signs/symptoms of: abdominal hemorrhage (following injection), hypersensitivity reactions, Cardiovascular disease, depression and Pituitary apoplexy (e.g., sudden headache, vomiting, visual or mental status changes, and, infrequently, cardiovascular collapse).
Drug Interactions	***Risk X: Avoid combination*** Corifollitropin Alfa, Indium 111. ***Risk D: Consider therapy modification*** Piflufolastat F18, Flotufolastat F18, Gallium Ga 68 PSMA-11.
Pregnancy and Lactation	• **Pregnancy:** Contraindicated. Goserelin can cause fetal harm and increase the risk of pregnancy loss. Non-hormonal methods of contraception should be employed during therapy. • **Lactation**: Contraindicated due to the potential adverse reactions in nursing infants.
Administration	**Subcutaneous administration** • Goserelin is an implant; therefore, do not attempt to eliminate air bubbles prior to injection (may displace implant). • Administer implant by inserting needle into the anterior abdominal wall below the navel line at a 30- to 45-degree angle in a continuous motion until the protective sleeve touches the patient's skin; grasp barrel at the finger grip and fully depress plunger. • Withdraw the needle and allow protective sleeve to slide and cover needle. Dispose of the syringe in an approved sharps collector. • Do not penetrate muscle or peritoneum. • Monitor for signs/symptoms of abdominal hemorrhage. **N.B.** Refer to manufacturer PIL for specific considerations**.**
Warnings/ Precautions	• **Cervical resistance:** Cervical resistance may be increased; use caution when dilating the cervix for endometrial ablation. • **Injection site injury:** Goserelin has been linked to injection site and vascular harm, including discomfort, hematoma, bleeding, and hemorrhagic shock (may require blood transfusions or surgical intervention). When giving medication to patients who have a low body mass index (BMI) or who are getting full dose anticoagulation, exercise special caution. • **Pituitary apoplexy**: Rare cases of pituitary apoplexy (secondary to pituitary gland infarction) have been observed within 1 hour to usually <2 weeks; may present as sudden headache, vomiting, visual or mental status changes, and, infrequently, cardiovascular collapse; immediate medical attention required. Pituitary tumors have been reported.

	• **Decreased bone density:** Decreased bone mineral density has been reported in females and males. In the majority of cases, recovery of bone loss occurs after cessation of therapy. • **Hypercalcemia**: Hypercalcemia has been reported in patients with bone metastases. Monitor and manage appropriately. • **Psychiatric effects:** Increased risk of depression that may be severe. Carefully monitor patients for the development or worsening of psychiatric symptoms particularly with known depression or history of depression patients. • **QT prolongation:** Androgen deprivation therapy may prolong the QT interval. Assess benefit risk ratio in patients with risk factors or receiving concomitant medicinal products that might prolong the QT interval. • **Tumor flare:** due to transient elevations in serum levels of estrogen (in patients with breast cancer) and testosterone (in patients with prostate cancer). A few patients had a transient exacerbation of their bone pain, which can be treated symptomatically. Isolated cases of exacerbation of disease symptoms which may include ureteral obstruction and spinal cord compression. Monitor patients at risk for complications of tumor flare. • **Hypersensitivity**: antibody formation and acute anaphylactic reactions have been reported with GnRH agonist analogues. • **Hyperglycemia** and an increased risk of developing diabetes have been reported in men receiving GnRH agonists. Monitor r blood glucose and/or glycosylated hemoglobin (HbA1c) periodically. • **Cardiovascular Diseases**: Increased risk of developing myocardial infarction, sudden cardiac death and stroke has been reported concomitantly with use of GnRH agonists in men.
Storage and Light Sensitivity	• Store between (15°C to 30°C). • Protect from light and moisture. **N.B.** Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• This drug may raise some hormone levels in your body during the first few weeks of taking it. Disease signs may get worse before getting better. • High blood sugar may happen with this drug. This drug may cause weak bones. Have your blood tests, and bone density checked as you told by your doctor. • Tell your doctor immediately if any signs of stroke, heart problems, or urination problems occurred. • For females, this drug stops you from having a period (menstrual bleeding). But use a non-hormone type of birth control as this drug may cause harm to an unborn baby.

2. Leuprolide

Generic Name	Leuprolide (Leuprorelin Acetate)
Dosage Form/Strengths	Lyophilized powder for I.M. injection: 3.75 mg, 11.25 mg, 22.5 mg.
Route of Administration	Intramuscular.
Pharmacologic Category	Antineoplastic Agent, Gonadotropin-Releasing Hormone Agonist. ATC Code: L02AE02
Indications	**N.B.** *Refer to literature and specific protocols for all indications.* **Prostate cancer** (3.75mg, 11.25mg, 22.5mg) - Metastatic prostate cancer. - Locally advanced prostate cancer, as an alternative to surgical castration. - As an adjuvant treatment to radiotherapy or neo-adjuvant treatment prior to radiotherapy in patients with high-risk localized or locally advanced prostate cancer. - As an adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression. **Treatment of pediatric patients with central precocious puberty** (3.75mg, 11.25mg). **Endometriosis** (3.75mg, 11.25mg) - Management of pain and lesions associated with endometriosis. - In combination with a Norethindrone acetate for initial management of the painful symptoms of endometriosis and management of recurrence of symptoms. **Breast cancer** (3.75mg, 11.25mg) - Advanced breast cancer suitable for hormonal manipulation, as treatment in pre- and perimenopausal women. - Early-stage breast cancer in pre-and perimenopausal women at higher risk of disease recurrence (young age, high-grade tumor, lymph node involvement), as adjuvant treatment in combination with Tamoxifen or an aromatase inhibitor. **Uterine fibroids** (3.75mg) , as preoperative management to reduce their size and associated bleeding. **Preservation of ovarian function** (3.75mg) in pre-menopausal women with neoplastic disease undergoing chemotherapy treatment that can cause premature ovarian insufficiency. It is not a replacement for standard fertility preservation methods. Treatment with a GnRH analogue should only be used after evaluation of benefit/risk ratio.
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols.* **Prostate cancer** **IM**: 3.75 mg every month, or 22.25 mg every 3 months.

	Duration: Usually continued till development of castrate-resistant prostate cancer. **Central precocious puberty in pediatrics** Children with a body weight ≥ 20 kg: **IM**: 3.75 mg once monthly or 11.25 mg every 3 months. Children with a body weight < 20 kg: **IM**: 1.88 mg once monthly or 5.64 mg every 3 months. Adjust dose to the next higher available form if inadequate hormonal and clinical suppression. **Duration**: Depends on the initial clinical parameters or as the treatment progresses (Final height prognosis, growth velocity, bone age and/or bone age acceleration). The bone age should be monitored during treatment at 6-12month intervals. **Endometriosis** **IM**: 3.75 mg every month, or 11.25 mg every 3 months. Initiate treatment during the first 5 days of the menstrual cycle. **Duration**: up to 6 months. Treatment may be extended for up to 12 months in chronic symptomatic endometriosis patients with coadministration of hormone replacement therapy (an estrogen and progestogen) to reduce bone mineral density loss and vasomotor symptoms. **Breast cancer** **IM**: 3.75 mg every month, or 11.2 5mg every 3 months. Initiate at least 6-8 weeks before starting aromatase inhibitor treatment. **Duration**: as adjuvant treatment in combination with other hormonotherapy is up to 5 years. **Uterine fibroids** **IM**: 3.75 mg every month. **Duration**: for 3-4 months, up to maximum 6 months. **Preservation of ovarian function** **IM**: 3.75 mg administered as a single intramuscular injection 2 weeks before starting chemotherapy then monthly for the duration of the chemotherapy treatment.
Dosage Adjustment	**N.B.** *Refer to protocol used for specific dose modifications.* **Altered Kidney Function: Adult** There are no dosage adjustments available. Not studied. **Dosing: Hepatic Impairment: Adult** There are no dosage adjustments available. Not studied.
Contra-indications	• Hypersensitivity to leuprolide, GnRH, GnRH-agonist analogs, or any component of the formulation. • Pregnancy. • Undiagnosed abnormal uterine bleeding (women).

Adverse Drug Reactions	**>10%** **Cardiovascular:** ECG changes (≤19%), edema (5% to 21%), flushing (children: 5%; adults: ≤78%), hypertension (children, adults: ≤15%), ischemia (≤19%) (See Table 1), peripheral edema (children, adults: ≤12%) **Dermatologic:** Diaphoresis (≤98%), pruritus (children: 11%; adults: 2% to 3%) **Endocrine & metabolic**: Decreased libido (3% to 11%), hot flash (≤98%), increased serum cholesterol (23%), increased serum triglycerides (12% to 32%), weight gain (children, adults: ≤13%), weight loss (≤13%) **Gastrointestinal:** Abdominal pain (children: 9% to 18%; adults: <1%), constipation (children: 6%; adults: ≤14%), diarrhea (children, adults: ≤16%), hematochezia (children: ≤13%), nausea (children: ≤13%; adults: ≤25%), vomiting (children: ≤13%; adults: ≤25%) **Genitourinary**: Testicular atrophy (4% to 20%), vaginitis (children: ≤3%; adults: 11% to 28%) **Hematologic & oncologic**: Bruise (children: ≤13%) **Local:** Bruising at injection site (children: ≤78%; adults: 3% to 12%), discomfort at injection site (children: ≤78%; adults: ≤19%), erythema at injection site (children: ≤78%; adults: 2% to 38%), injection-site reaction (children: ≤78%; adults: ≤14%, including abscess at injection site), pain at injection site (children: ≤78%; adults: ≤19%), swelling at injection site (children: ≤78%), warm sensation at injection site (children: ≤78%) **Nervous system:** Asthenia (children: <1%; adults: ≤18%), depression (children: ≤22%; adults: ≤31%) (See Table 2), dizziness (children: <1%; adults: ≤16%), emotional lability (children: ≤22%; adults: ≤31%), fatigue (≤18%), headache (children: 2% to 33%; adults: ≤65%), insomnia (children, adults: ≤31%), lethargy (≤13%), malaise (≤18%), migraine (≤65%), mood changes (children: ≤22%; adults: ≤5%), pain (3% to 33%), psychiatric signs and symptoms (children: ≤22%; including affective disorder, aggressive behavior, auditory hallucinations, crying, disruptive mood dysregulation disorder, and trichotillomania), sleep disorder (≤31%), vertigo (≤16%) **Neuromuscular & skeletal**: Arthropathy (children: <2%; adults: 4% to 16%), increased creatinine phosphokinase in blood specimen, musculoskeletal pain (children: <1%; adults: ≤11%) **Respiratory:** Cough (children, adults: 1% to 13%), epistaxis (children, adults: ≤13%), flu-like symptoms (children: <2%; adults: ≤21%), nasopharyngitis (children, adults: ≤22%), upper respiratory tract infection (children: 6%; adults: ≤21%) **Miscellaneous:** Fever (children: 13% to 17%; adult: <5%). **1% to 10%** **Cardiovascular:** Acute myocardial infarction (<5%), angina pectoris (<5%), atrial fibrillation (<5%), bradycardia (children, adults: <5%), cardiac arrhythmia (<5%), chest pain (children: 4%), coronary artery disease (≤6%), deep vein

thrombophlebitis (<5%), heart failure (1%), heart murmur (3%), hypotension (children; adults: <5%), palpitations (<5%), peripheral vascular disease (<2%), phlebitis (≤2%), pitting edema (≤5%), syncope (children, adults: <5%), tachycardia (<5%), thrombosis (≤2%), varicose veins (<5%), vasodilation (children: 2%).

Dermatologic: Acne vulgaris (children: ≤3%; adults: ≤10%), allergic skin reaction (≤10%), alopecia (children, adults: ≤4%), body odor (children, adults: <5%), cellulitis (<5%), cold and clammy skin (4%), dermatitis (5%), ecchymoses (<5%), erythema multiforme (children: ≤3%), hair disease (<5%), hyperhidrosis (children: 4%), hyperpigmentation (including dyschromia: <5%), leukoderma (children: <2%), malignant melanoma, nail disease (children, adults: <5%), night sweats (3%), seborrhea (children: ≤3%), skin carcinoma (including ear: <5%), skin hypertrophy (children: <2%), skin lesion (<5%), skin rash (children, adults: 7%), xeroderma (<5%).

Endocrine & metabolic: Androgen-like effect (females: ≤4%), decreased HDL cholesterol (2% to 10%), decreased serum albumin (≥5%), decreased serum bicarbonate (≥5%), decreased serum total protein (≥5%), dehydration (8%), diabetes mellitus (children; adults: <5%), feminization (children: <2%), goiter (children, adults: <5%), growth retardation (children: <2%), gynecomastia (children, adults: ≤7%), hirsutism (children: <2%), hyperglycemia (≥5%), hyperphosphatemia (≥5%), hyperuricemia (≥5%), hypoglycemia (<5%), increased lactate dehydrogenase (≥5%), increased LDL cholesterol (8%), increased serum calcium (<5%), increased thirst (<5%), increased uric acid (≥5%), loss of libido (<2%), menstrual disease (children, adults: ≤2%).

Gastrointestinal: Abdominal distention (<5%), anorexia (6%), change in appetite (4%), colitis (≤3%), duodenal ulcer (<5%), dysgeusia (<5%), dyspepsia (children, adults: <4%), dysphagia (children, adults: <5%), eructation (<5%), flatulence (≤4%), gastroenteritis (≤3%), gastrointestinal hemorrhage (<5%), gingival hemorrhage (<5%), gingivitis (children, adults: <5%), hernia of abdominal cavity (<5%), hiccups (<5%), increased appetite (children, adults: <5%), intestinal obstruction (<5%), melanosis (<5%), mucous membrane abnormality (reaction: ≤4%), peptic ulcer (<5%), periodontal abscess (<5%), rectal polyp (<5%), xerostomia (<5%).

Genitourinary: Balanitis (<5%), bladder carcinoma (<5%), bladder spasm (<5%), breast changes (≤6%), breast disease (children: <2%), breast hypertrophy (children; adults: <5%), breast tenderness (children, adults: ≤7%), cervical neoplasm (children: <2%), cervix disease (children: <2%), decreased prostatic acid phosphatase (≥5%), difficulty in micturition (<2%), dysmenorrhea (children: <2%), dysuria (≤6%), epididymitis (<5%), erectile dysfunction (<2%), hematuria (≤6%), hemorrhagic cystitis (including cystitis: ≤6%), impotence (males: 4% to 5%), increased prostatic acid phosphatase (≥5%), lactation (<5%), mastalgia (≤7%), nocturia (1% to 6%), oliguria (<2%), penile disease (<5%), pollakiuria (2%), prostatic disease (<5%), reduction in penile size (<2%), sexual disorder

(accelerated sexual maturity: children: <2%), testicular disease (<5%), testicular pain (2%), urinary frequency (≤6%), urinary incontinence (children, adults: <5%), urinary retention (<2%), urinary tract infection (≤6%), urinary tract obstruction (<5%), urinary tract pain (1%), urinary urgency (≤6%), vaginal discharge (children: ≤3%), vaginal hemorrhage (children: ≤3%).

Hematologic & oncologic: Anemia (≤6%), carcinoma (<5%), eosinophilia (≥5%), increased erythrocyte sedimentation rate (children: <2%), leukopenia (≥5%), lymphadenopathy (<5%), lymphedema (<5%), neoplasm (<5%), prolonged partial thromboplastin time (≥5%), prolonged prothrombin time (≥5%), purpuric disease (children: <2%), second primary malignant neoplasm (including basal cell carcinoma of skin, malignant melanoma, non-Hodgkin lymphoma, pulmonary neoplasm), squamous cell carcinoma (7%), thrombocytosis (≥5%), tumor flare (children: <2%).

Hepatic: Abnormal hepatic function tests (≥5%), hepatomegaly (<5%), increased gamma-glutamyl transferase (≥5%), increased serum alanine aminotransferase (≥5%), increased serum aspartate aminotransferase (≥5%), increased serum transaminases (3%).

Hypersensitivity: Hypersensitivity reaction (children, adults: <5%).

Immunologic: Increased ANA titer (children: <2%).

Infection: Abscess (<5%), herpes zoster infection (<5%), infection (children, adults: ≤5%).

Local: Induration at injection site (children, adults:<3%), injection-site pruritus (≤9%).

Nervous system: Abnormality in thinking (<5%), agitation (<5%), altered sense of smell (<2%), amnesia (<5%), anxiety (≤8%), chills (<5%), confusion (<5%), delusion (<5%), dementia (<5%), drowsiness (children: <2%), hypoesthesia (<5%), irritability (including impatience: 2%), loss of consciousness (<5%), memory impairment (6%), nervousness (children: <2%; adults: ≤8%), neuropathy (<5%), numbness (<5%), paralysis (children; adults: <5%), paresthesia (≤8%), peripheral neuropathy (children; adults: <5%), personality disorder (<5%), rigors (<2%), tremor (<2%), voice disorder (<5%).

Neuromuscular & skeletal: Amyotrophy (<2%), arthralgia (children: <2%; adults: ≤9%), arthritis (≤1%), back pain (children, adults: ≤7%), bone disease (temporal bone swelling: <5%), hyperkinetic muscle activity (children: <2%), limb pain (children, adults: ≤10%), lower limb cramp (≤2%), myalgia (can be severe: children: <2%; adults: ≤8%), myopathy (children: <2%), neck pain (<5%), ostealgia (2% to 5%), pathological fracture (children, adults: <5%).

Ophthalmic: Amblyopia (<5%), blepharoptosis (<5%), blurred vision (<5%), conjunctivitis (<5%), dry eye syndrome (<5%), visual disturbance (children, adults: <5%).

Otic: Tinnitus (<5%).

Renal: Decreased urine specific gravity (≥5%), increased blood urea nitrogen, increased serum creatinine, increased urine specific gravity (≥5%).

	Respiratory: Asthma (children, adults: <5%), bronchitis (<5%), bronchospasm (children: 6%), chronic obstructive pulmonary disease (5%), dyspnea (≤5%), dyspnea on exertion (1% to 5%), hemoptysis (<5%), hypoxia (<5%), increased bronchial secretions (<5%), paranasal sinus congestion (5%), pharyngitis (children, adults: <5%), pleural effusion (<5%), pleural rub (<5%), pneumonia (<5%), productive cough (children: 6%), pulmonary edema (<5%), pulmonary emphysema (<5%), pulmonary fibrosis (<5%), rhinitis (children, adults: <5%), sinus headache (≤8%), sinusitis (children, adults: <5%). **Miscellaneous:** Abnormal healing (<5%), cyst (<5%), inflammation (<5%).
Monitoring Parameters	• Monitor for signs/symptoms of hypersensitivity. • Pregnancy exclusion test before starting treatment. • CBC (baseline, monthly for 4 months then every 6 months). • Bone mineral density (particularly in women who have additional risk factors for osteoporosis). • Hepatic function test. • Asses for cardiovascular diseases prior to treatment and during treatment: Blood pressure, heart rate and Prothrombin time test. • FSH and estradiol prior to starting aromatase inhibitor treatment (every 3 months) during combination therapy with leuprorelin and an aromatase inhibitor. • Monitor for development or worsening of psychiatric symptoms. **For prostate cancer** • Monitor Serum testosterone, prostate-specific antigen (PSA) periodically. **For central precocious puberty** • The bone age (at 6-12month intervals). • Gonadotropin-releasing hormone (GnRH) test. • Weight (baseline and periodically).
Drug Interactions	***Risk X: Avoid combination*** Corifollitropin Alfa, Indium 111 Capromab Pendetide. ***Risk D: Consider therapy modification*** Flotufolastat F18, Gallium Ga 68 PSMA-11, Piflufolastat F18.
Pregnancy and Lactation	**Pregnancy** Contraindicated. Fetal malformation and spontaneous abortion may occur—reproductive toxicity in animal studies. **Lactation**: No human data. It is not recommended due to the risk of serious adverse reactions.
Administration	• **Hazardous agent** (NIOSH 2016 [group 1]): Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. • **IM**: Administer as a single injection into the gluteal area, anterior thigh, or deltoid. The injection site should be alternated. Administer immediately after preparation. • Do not use a combination of doses due to different release characteristics. Do not use a combination of syringes to achieve a particular dose. Do not

	administer IV. • The reconstituted product is a suspension of milky, white color appearance. **N.B**. Refer to manufacturer PIL if any other specific considerations.
Warnings/ Precautions	**Cardiovascular Diseases**: Increased risk of myocardial infarction, sudden cardiac death, and stroke has been reported in association with the use of GnRH analogs in men. Monitor for cardiovascular disease and manage according to current clinical practice. Leuprorelin should be used with caution in the presence of, cardiovascular disease, thromboembolism, edema, bleeding disorders, thrombocytopenia or on treatment with anticoagulants. **Psychiatric events**: In patients treated with GnRH agonists. Events include mood changes and depression. Monitor for development or worsening of psychiatric symptoms. **Convulsions:** Observed in patients with a history of epilepsy, cerebrovascular disorders, central nervous system tumors and in patients with concomitant medications that have been associated with seizures e.g. Bupropion and SSRIs. Seizures also occurred in patients without predisposing conditions. **Metabolic changes**: Reduction in glucose tolerance or aggravation of preexisting diabetes may occur. Diabetic patients may require more frequent monitoring of blood glucose during treatment. **Initial Rise of Gonadotropins and Sex Steroid Levels**: During the early phase of therapy, gonadotropins and sex steroids may rise above baseline because of the initial stimulatory effect of the drug. **In children**: An increase in clinical signs and symptoms of puberty, including vaginal bleeding, may be observed during the first weeks of therapy or after subsequent doses. **In men:** - Exacerbation of the tumor growth resulting in temporary worsening of prostate cancer symptoms. These symptoms usually subside on continuation of therapy. To reduce the risk of flare, an anti-androgen may be administered 3 days before leuprorelin acetate therapy and continuing for the first two to three weeks of treatment. - Urethral obstruction and spinal cord compression or metastatic vertebral lesions have been observed, which may contribute to paralysis with or without fatal complications. Monitor high-risk patients carefully in the first few weeks and consider prophylactic antiandrogen. - A small number of patients may experience a temporary increase in bone pain which can be managed symptomatically. **Abnormal bleeding in women:** Before administration, undiagnosed vaginal bleeding must be investigated, diagnosis confirmed, and suitable management initiated. **Uterine fibroids**: Exclude an ovarian mass before starting therapy. Consider a

	one-month trial period on iron alone, as some women will respond to iron alone. If inadequate response, Leuprolide may be added. In women with submucous fibroids, severe vaginal bleeding following administration of leuprorelin has been reported. Patients should be warned of the possibility of abnormal bleeding or pain in case earlier surgical intervention is required. **Advanced and early breast cancer**: Premenopausal status should be confirmed following chemotherapy and before initiation of Leuprorelin, by blood concentrations of estradiol and FSH within the reference ranges for premenopausal women, to avoid unnecessary treatment with Leuprorelin if chemotherapy has already induced menopause. Ovarian suppression should be confirmed by low blood concentrations of FSH and estradiol prior to starting aromatase inhibitor treatment and measurements should be repeated every three months during combination therapy with Leuprorelin and an aromatase inhibitor. **Bone density:** A small loss in bone density, some of which may not be reversible in patients with endometriosis or uterine fibroids due to the hypo-estrogenic state induced by therapy. Caution in high-risk patients. While in children, after cessation of treatment subsequent bone mass accrual is preserved. **Hypersensitivity reactions**: Discontinue treatment immediately if the patient develops any signs of anaphylactic reaction (dyspnea, asthma, rhinitis, angioneurotic edema or glottis, hypotension, urticaria, rash, pruritus or interstitial pneumonitis). **Idiopathic intracranial hypertension**: Idiopathic intracranial hypertension (pseudotumor cerebri) has been reported in patients receiving Leuprorelin. Warn the patient for signs that include severe or recurrent headaches, vision disturbances, and tinnitus. If this occurs, consider discontinuation of Leuprorelin. **Effect on QT/QTc Interval:** Androgen deprivation therapy may prolong the QT/QTc interval. Asses the benefit-risk ratio in high-risk patients and in patients receiving concomitant medicinal products that might prolong the QT interval. Electrolyte abnormalities should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes.
Storage and Light Sensitivity	• Keep between 15°C and 30°C. Protect from light. • Once reconstituted with solvent, suspension should be administered immediately. **N.B.** Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• The most common side effects associated with Leuprolide are hot flashes, pain (especially joint pain and back pain), injection site pain and fatigue. • This drug may raise some hormone levels in your body during the first few weeks of taking it. Disease signs may get worse before getting better. • Have your blood work and bone density checked regularly. • Check your blood sugar regularly.

- A chance of heart problems has been noted with the use in males. The chance is low but get medical help right away if you have chest pain or pressure, weakness on 1 side of the body, trouble speaking or thinking, change in balance, drooping on 1 side of the face, or change in eyesight.

IMMUNE MODULATORY DRUG

1. Lenalidomide

Generic Name	Lenalidomide
Dosage Form/ Strengths	Capsules: 5mg, 10mg, 15mg, 25mg.
Route of Administration	Oral
Pharmacologic Category	Angiogenesis Inhibitor; Antineoplastic Agent ATC Code: L04AX04.
Indications	**N.B.** *Refer to literature and specific protocols for all indications*. • **Multiple Myeloma.** - Maintenance therapy following autologous hematopoietic stem cell transplantation (auto-HSCT) as monotherapy. - Treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant, in combination with dexamethasone, bortezomib and dexamethasone, or melphalan and prednisone. - Treatment of multiple myeloma in adult patients who have received at least one prior therapy, in combination with dexamethasone. • **Follicular lymphoma:** Treatment of adult patients with previously treated follicular lymphoma (Grade 1 – 3a), in combination with rituximab (anti-CD20 antibody). • **Transfusion-dependent anemia** due to low- or intermediate-1-risk **myelodysplastic syndromes (MDS)** associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities. • **Mantle cell lymphoma (MCL)** whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib. • **Marginal zone lymphoma (MZL),** that is Previously treated, in combination with a rituximab product.
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols.* • **Multiple Myeloma:** - <u>In patients who are not eligible for transplant.</u> **-** *In combination with dexamethasone* Do not start Lenalidomide if the Absolute Neutrophil Count (ANC) is < 1.0 x 10^9 /L, and/or platelet counts are < 50 x 10^9 /L. **Oral**: 25 mg once daily on Days 1-21 of repeated 28-day cycles. Dexamethasone dose is 40 mg orally once daily on days 1, 8, 15 and 22 of repeated 28-day cycles. Continue until disease progression or intolerance. **-** *In combination with bortezomib and dexamethasone followed by lenalidomide and dexamethasone* Do *not* start Lenalidomide if the Absolute Neutrophil Count (ANC) is < 1.0 x 10^9 /L, and/or platelet counts are < 50 x 10^9 /L. **Oral**: 25 mg once daily days 1-14 of each 21-day cycle in combination with

bortezomib and dexamethasone. Bortezomib should be administered via subcutaneous injection (1.3 mg/m^2) twice weekly on days 1, 4, 8 and 11 of each 21-day.

Up to eight 21-day treatment cycles (24 weeks of initial treatment) are recommended.

- *In combination with melphalan and prednisone*

Do not start Lenalidomide if the ANC is < 1.5 x 10^9 /L, and/or platelet counts are < 75 x 10^9 /L.

Oral: 10 mg once daily on days 1 to 21 of repeated 28-day cycles for up to 9 cycles, melphalan 0.18 mg/kg orally on days 1 to 4 of repeated 28-day cycles, prednisone 2 mg/kg orally on days 1 to 4 of repeated 28-day cycles.

Maintenance therapy in patients who have undergone autologous stem cell transplantation (ASCT)

Do not start Lenalidomide if Absolute Neutrophil Count (ANC) is < 1.0 x 10^9 /L, and/or platelet counts are < 75 x 10^9 /L.

Oral: 10 mg once daily continuously on Days 1-28 of repeated 28-day cycles given until disease progression or intolerance. After 3 cycles of lenalidomide maintenance, the dose can be increased to 15 mg orally once daily if tolerated.

Multiple myeloma with at least one prior therapy

Do not start Lenalidomide if the ANC < 1.0 x 10^9 /L, and/or platelet counts < 75 x 10^9 /L or, dependent on bone marrow infiltration by plasma cells, platelet counts < 30 x 10^9 /L.

Oral: 25 mg once daily on days 1 to 21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for the first 4 cycles of therapy and then 40 mg once daily on days 1 to 4 every 28 days.

- **Follicular lymphoma.**

Do not start Lenalidomide if the ANC is < 1 x 10^9/L, and/or platelet count < 50 x 10^9/L, unless secondary to lymphoma infiltration of bone marrow.

Oral: 20 mg, once daily on days 1 to 21 of repeated 28-day cycles for up to 12 cycles of treatment. The recommended starting dose of rituximab is IV 375 mg/m^2 every week in Cycle 1 (days 1, 8, 15, and 22) and day 1 of every 28-day cycle for cycles 2 through 5.

- **Marginal Zone Lymphoma.**

Oral: 20 mg once daily on Days 1-21 of repeated 28-day cycles for up to 12 cycles.

- **Myelodysplastic Syndromes**

10 mg once daily.

- **Mantle Cell Lymphoma (MCL)**

Oral: 25 mg once daily on Days 1-21 of repeated 28-day cycles. Continue until disease progression or unacceptable toxicity.

Pediatrics: Lenalidomide should not be used in children and adolescents till 18 years because of safety concerns.

Dosage Adjustment

N.B. *Refer to protocol used for specific dose modifications.*

Dosage: Renal impairment

Renal Function	Combination therapy for Multiple Myeloma and Mantle Cell Lymphoma	Follicular lymphoma or Marginal Zone Lymphoma	Maintenance Therapy Following Auto-HSCT for Multiple Myeloma and for Myelodysplastic Syndromes
Crcl 30 to 60 mL/min	10 mg once daily. For MM, consider escalating the dose to 15 mg after 2 cycles if no dose-limiting toxicity occurred.	10 mg once daily. Consider escalating the dose to 15 mg after 2 cycles if no dose-limiting toxicity occurred.	5 mg once daily.
Crcl below 30 mL/min (not requiring dialysis)	15 mg every other day	5 mg once daily	2.5 mg once daily
Crcl below 30 mL/min (requiring dialysis)	5 mg once daily. On dialysis days, administer the dose following dialysis.	5 mg once daily. On dialysis days, administer the dose following dialysis.	2.5 mg once daily. On dialysis days, administer the dose following dialysis

Dosing: Hepatic Impairment

- Mild hepatic impairment: No dose adjustments are needed.
- Moderate to severe hepatic impairment: No data is available.

Hepatotoxicity during treatment: Interrupt lenalidomide for abnormal hepatic function tests; may consider resuming treatment at a lower dose upon return to baseline.

Dosing: Hematologic Toxicities

Multiple myeloma

- If platelets fall to <30 x 10^9 /L: Interrupt lenalidomide treatment and resume

	at lower dose level (dose level -1) when returns to ≥ 30 x 10^9 /L. • If Absolute neutrophil count (ANC) falls to < 0.5 x 109 /L: Interrupt lenalidomide treatment and resume at starting dose when ANC returns to ≥ 0.5 x 109 /L with no other hematological toxicities or decrease to dose level -1 if other hematological toxicities appeared. **Follicular lymphoma (FL), Mantle cell lymphoma (MCL), or Marginal Zone Lymphoma (MZL)** • If platelets Fall to < 50 x 10^9 /L: Interrupt lenalidomide and Resume at next lower dose level when returns to ≥ 50 x 10^9 /L. • If ANC falls below 1 x 10^9 /L for at least 7 days OR falls below 1 x 10^9 /L with an associated temperature at least 38.5°C OR Falls below 0.5 to 1 x 10^9 /L: Interrupt lenalidomide and check CBC weekly and Resume at next lower dose level (dose level -1) if returns to at least 1 x 10^9 /L. **Myelodysplastic Syndromes** • If thrombocytopenia develops WITHIN 4 weeks: If platelets fall to 50% of baseline, interrupt treatment and resume at 5mg daily when returns to at least 30 x 10^9 /L. • If thrombocytopenia develops AFTER 4 weeks: If platelets fall below 30 x 10^9 /L or below 50 x 10^9 /L with platelet transfusions, resume at 5mg daily when it returns to at least 30 x 10^9 /L. • If neutropenia develops WITHIN 4 weeks: If ANC falls below 0.75 x 10^9 /L (If baseline ANC is at least 1 x 10^9 /L) or below 0.5 x 10^9 /L (if baseline ANC is below 1 x 10^9 /L) interrupt treatment and resume at 5mg daily when returns to at least 1 or 0.5 x 10^9 /L respectively. • If neutropenia develops AFTER 4 weeks: If ANC falls below 0.5 x 10^9 /L for at least 7 days or below 0.5 x 10^9 /L associated with fever (at least 38.5°C) Interrupt treatment, resume at 5 mg if returns to at least 0.5 x 10^9 /L. **Dermatologic toxicity**: Consider discontinuation Lenalidomide in grade 2 or 3 skin rash. Discontinue at grade 4 rash or hypersensitivity. **Tumor flare reaction** Grade 1 or 2: Continue therapy with caution; may consider symptom management with NSAIDs or limited duration corticosteroids and/or narcotic analgesic therapy. Grade 3 or 4: Withhold lenalidomide and symptom management; resume when tumor flare reaction resolved to ≤ grade 1.
Contra-indications	• Hypersensitivity to the active substance or to any of the excipients. • Pregnancy.
Adverse Drug Reactions	**>10%** **Cardiovascular**: Peripheral edema (MCL, MDS: 16% to 20%). **Dermatologic**: Pruritus (MCL: 17%; MDS: 42%), skin rash (MCL, MDS: 22% to 36%; MM-auto-HSCT: 8%), xeroderma (MDS, MM-auto-HSCT: 11% to 14%). **Endocrine & metabolic**: Hypokalemia (4% to 13%), weight loss (MCL: 13%)

Gastrointestinal: Abdominal pain (10% to 12%), constipation (13% to 24%), decreased appetite (MCL: 14%), diarrhea (MCL: 31%; MDS, MM-auto-HSCT: 39% to 49%; grades 3/4: 2% to 6%), gastroenteritis (MM-auto-HSCT: 23%), nausea (MCL, MDS: 24% to 30%; MM-auto-HSCT: 11%; grades 3/4: <4%), vomiting (MCL, MDS: 10% to 12%; grades 3/4: ≤1%).
Genitourinary: Urinary tract infection (4% to 11%).
Hematologic & oncologic: Anemia (MCL: 31%; MDS, MM-auto-HSCT: 9% to 11%, grades 3/4: 4% to 11%), leukopenia (MCL, MDS: 8% to 15%; MM-auto-HSCT: 32%; grades 3/4: MCL, MDS: 5% to 7%; MM-auto-HSCT: 24%), neutropenia (MCL: 49%; MDS, MM-auto-HSCT: 59% to 61%; grades 3/4: 43% to 54%), thrombocytopenia (MCL, MM-auto-HSCT: 24% to 36%; MDS: 61%; grades 3/4: MCL: 28%; MDS: 50%; MM-auto-HSCT: 13%).
Infection: Influenza (MM-auto-HSCT: 13%).
Nervous system: Asthenia (MCL, MDS: 14% to 15%; MM-auto-HSCT: 30%), dizziness (MDS: 20%), fatigue (MCL, MDS: 31% to 34%; MM-auto-HSCT: 11%), headache (MDS: 20%; MM-auto-HSCT: 9%), paresthesia (MM-auto-HSCT: 13%).
Neuromuscular & skeletal: Arthralgia (MCL: 8%; MDS: 22%), back pain (MCL, MDS: 13% to 21%), limb pain (MDS: 11%), muscle cramps (MDS: 18%), muscle spasm (MCL: 13%; MM-auto-HSCT: 33%)
Respiratory: Bronchitis (MDS: 6%; MM-auto-HSCT: 47%), cough (20% to 28%), dyspnea (including exacerbations: MCL, MDS: 17% to 18%; MM-auto-HSCT: 6%), epistaxis (MDS: 15%), nasopharyngitis (MDS: 23%; MM-auto-HSCT: 35%), pharyngitis (MDS: 16%), pneumonia (11% to 17%; can be lobar pneumonia), rhinitis (MDS, MM-auto-HSCT: 7% to 15%), sinusitis (MDS, MM-auto-HSCT: 8% to 14%; can be acute sinusitis), upper respiratory tract infection (11% to 15%).
Miscellaneous: Fever (20% to 23%).

1% to 10%

Cardiovascular: Acute myocardial infarction (MCL: ≥2%), chest pain (MDS: 5%), deep vein thrombosis (MCL, MM-auto-HSCT: 2% to 4%), edema (MDS: 10%), heart failure (MCL), hypertension (MDS: 6%), hypotension (MCL: 7%), palpitations (MDS: 5%), pulmonary embolism (MCL, MM-auto-HSCT: 1% to 2%), supraventricular tachycardia (MCL: ≥2%), swelling of extremities (MDS: 8%), syncope (MDS: grades 3/4: 1%).
Dermatologic: Basal cell carcinoma of skin (MCL: ≥2%), cellulitis (MCL, MDS: 2% to 5%), diaphoresis (MDS: 7%), ecchymoses (MDS: 5%), erythema of skin (MDS: 5%), night sweats (MDS: 8%), squamous cell carcinoma of skin (MCL: 3%).
Endocrine & metabolic: Dehydration (MCL: 7%), hypocalcemia (MCL: 3%), hypomagnesemia (MDS: 6%), hyponatremia (MCL: 2%), hypothyroidism (MDS: 7%).
Gastrointestinal: Anorexia (MDS: 10%), Clostridioides difficile colitis (MCL:

	≥2%), dysgeusia (MDS: 6%), oral herpes simplex infection (MCL), upper abdominal pain (MDS, MM-auto-HSCT: 7% to 8%), xerostomia (MDS: 7%). **Genitourinary**: Dysuria (MDS: 7%). **Hematologic & oncologic**: Bruise (MDS: 8%), febrile neutropenia (2% to 6%; grades 3/4: 2% to 6%), granulocytopenia (MDS: grades 3/4: 2%), lymphocytopenia (MCL, MM-auto-HSCT: 4% to 7%; grades 3/4: 4%), myelodysplastic syndrome (MM-auto-HSCT: 1%; grades 3/4: <1%), pancytopenia (MM-auto-HSCT: 4%; MDS, MM-auto-HSCT: grades 3/4: 2%), tumor flare (MCL: 10%). **Hepatic**: Hyperbilirubinemia (MM-auto-HSCT: 1%), increased serum alanine aminotransferase (MDS: 8%). **Infection**: Bacteremia (MCL: 1%), herpes zoster infection (including reactivation; MM-auto-HSCT: 10%), infection (MM-auto-HSCT: 6%), sepsis (MCL, MM-auto-HSCT: 1% to 2%). **Nervous system**: Chills (MCL), depression (MDS: 5%), hypoesthesia (MDS: 7%), insomnia (MDS: 10%), lethargy (MCL), myasthenia (MCL: 6%), pain (MDS: 7%), peripheral neuropathy (MDS, MM-auto-HSCT: 5% to 10%; grades 3/4: 1%), rigors (MDS: 6%), vertigo (MCL). **Neuromuscular & skeletal**: Myalgia (MDS, MM-auto-HSCT: 6% to 9%) **Renal**: Renal failure syndrome (MCL: 4%). **Respiratory**: Chronic obstructive pulmonary disease (MCL: ≥2%), Dyspnea on exertion (MDS: 7%), hypoxia (MCL: 2%), oropharyngeal pain (MCL: 10%), pleural effusion (MCL: 7%), respiratory distress (MCL: 1%), respiratory tract infection (MM-auto-HSCT: 3%), rhinorrhea (MM-auto-HSCT: 5%). **Miscellaneous**: Multi-organ failure (MDS: grades 3/4: 1%).
Monitoring Parameters	• CBC with differential and platelets. • Renal and liver functions. • Thyroid function tests (Baseline and ongoing). • Monitor patients with thromboembolism risk factors. • Monitor for signs and symptoms of infection (if neutropenic), bleeding, hepatotoxicity, secondary malignancies, visual disorders. • Monitor for tumor flare reaction in patients with lymphomas.
Drug Interactions	***Risk X: Avoid combination*** Abatacept, Abrocitinib, Anakinra, Baricitinib, BCG Products, Brivudine, Canakinumab, Certolizumab Pegol, Chikungunya Vaccine (Live), Chloramphenicol (Systemic), Cladribine, Dengue Tetravalent Vaccine (Live), Deucravacitinib, Dipyrone, Etrasimod, Fexinidazole, Filgotinib, Mumps-Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Natalizumab, Pembrolizumab, Pimecrolimus, Poliovirus Vaccine (Live/Trivalent/Oral), Rilonacept, Ritlecitinib, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Typhoid Vaccine, Upadacitinib, Vaccines (Live), Vedolizumab, Yellow Fever Vaccine. ***Risk D: Consider therapy modification***

	Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), Deferiprone, Denosumab, Dexamethasone (Systemic), Influenza Virus Vaccines, Leflunomide, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating). ***Notes*** **Digoxin:** Monitor digoxin plasma levels as it may increase with multiple doses of lenalidomide (10 mg daily). **Warfarin**: Monitor for PT and INR during treatment in patients taking concomitant warfarin. **Statins**: Additive action. Enhanced clinical and laboratory monitoring is needed during the first weeks of treatment.
Pregnancy and Lactation	**Pregnancy:** Contraindicated due to Teratogenic effect. Effective contraception must be used. **Lactation**: Not recommended due to the potential secretion into breast milk and potential adverse reactions.
Administration	**Hazardous agent (NIOSH 2016 [group 2]):** Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage. **Administration: Oral** • Administer at about the same time each day with water. • Administer with or without food. • Swallow capsule whole. • Do not break, open, or chew. • Missed doses: May administer a missed dose if within 12 hours of usual dosing time. If exceeded 12 hours, patient should skip the missed dose and resume usual dosing. • Patient should **not** take 2 doses to make up for a missed dose.
Emetogenicity	Adults: Minimal or low (<30%).
Warnings/ Precautions	**CNS Effect** May result in weariness or dizziness; advise patients not to engage in activities requiring mental alertness, such as operating machinery or driving. **Tumor Flare Reaction** Treatment of lymphomas and chronic lymphocytic leukemia (CLL) with lenalidomide has shown tumor flare reactions, including fatalities; clinical presentation includes low grade fever, discomfort, rash, and painful lymph node enlargement. **Thyroid Disorders** Both hypothyroidism and hyperthyroidism have been reported. Measure initial thyroid function and during therapy. **Venous and Arterial Thromboembolism**

- Significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as risk of myocardial infarction and stroke in patients with multiple myeloma receiving lenalidomide with dexamethasone. Anti-thrombotic prophylaxis is recommended.
- Erythropoietin stimulating agents (ESAs) and estrogens should only be used in patients receiving lenalidomide after weighing the benefits and risks because they may raise the risk of thrombosis even more.

Hematologic Toxicity

- Significant thrombocytopenia and neutropenia can be brought on by Lenalidomide. Observe patients experiencing neutropenia for indications of infection. Encourage patients to keep an eye out for any bleeding or bruises, particularly if they are taking concurrent medications that could raise their risk of bleeding.
- Periodically, patients on Lenalidomide should undergo an evaluation of their total blood counts.

Myocardial infarction

- Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors and within the first year when used in combination with dexamethasone.
- Patients with risk factors including prior thrombosis event, smoking, hypertension, and hyperlipidemia should be closely monitored.

Renal impairment

Use with caution in patients with kidney impairment; may experience an increased rate of toxicities due to reduced clearance and increased half-life.

Mantle cell lymphoma

A higher risk of early mortality (within 20 weeks) in with MCL patients. High tumor burden, high WBC count (≥10,000/mm3) at baseline, and mantle cell lymphoma international prognostic index (MIPI) score at diagnosis are risk factors for early mortality.

Multiple Myeloma

Two clinical trials found that patients with multiple myeloma who got pembrolizumab along with a thalidomide analogue and dexamethasone experienced a higher death rate.

Stem Cell Mobilization

Treatment with Lenalidomide (≥4 cycles) may reduce the amount of CD34+ cells collected for autologous hematopoietic cell transplantation, which leads to stem cell mobilization. Consider early referral to transplant center.

Embryo-Fetal Toxicity

Thalidomide and Lenalidomide share structural similarities. Serious, potentially fatal birth abnormalities to those reported with thalidomide were caused by lenalidomide.

	Severe Cutaneous Reactions Including Hypersensitivity Reactions • There have been reports of angioedema and severe cutaneous responses, such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), and drug reaction with eosinophilia and systemic symptoms (DRESS). A cutaneous reaction (rash, exfoliative dermatitis, fever), eosinophilia, lymphadenopathy, and/or systemic consequences (hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis) can all be signs of DRESS. • Angioedema, Grade 4 rash, exfoliative or bullous rash, or if SJS, TEN, or DRESS is suspected—all require the cessation of Lenalidomide, which should not be restarted after these reactions. **Hepatotoxicity** • Hepatic failure, including fatal cases, has occurred in patients treated with Lenalidomide in combination with dexamethasone. • The mechanism of drug-induced hepatotoxicity is unknown. Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. • Monitor liver enzymes periodically. Stop Lenalidomide upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.
Storage and Light Sensitivity	• Store between 15°C to 30°C. • Protect from light and moisture. **N.B.** Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• This medicine may decrease blood cell counts. Avoid infection and bleeding causes. • Avoid getting pregnant during treatment which is teratogenic. • Tell your Physician if you are lactose intolerant or taking any medications or herbals. • Severe cardiac problems occurred more frequently, contact your healthcare providers. Call your doctor if you experience shortness of breath, chest pain or arm/leg swelling. • In case you have any of the following symptoms: a fast or irregular heartbeat, fainting, difficulty urinating, cramps or weakness in your muscles, upset stomach, vomiting, diarrhea, don't hesitate to contact your doctor. • If you experience any of the following symptoms: sores in your mouth, throat, nose, or eyes; red, swollen, blistered, or peeling skin; or red or irritated eyes. Get medical attention right once. • Worsening of your tumor (tumor flare reaction) has happened with this drug. Sometimes, this has been deadly. Tell your doctor right away if you have swollen glands, fever, pain, or rash.
Pharmaco-	• **Chromosome 5q Deletion**

genomics	May alter Pharmacodynamics of lenalidomide. Genetic testing is required.

MISCELLANEOUS

1. Hydroxycarbamide (Hydroxyurea)

Generic Name	Hydroxyurea
Dosage Form/ Strengths	Capsule: 500mg
Route of Administration	Oral
Pharmacologic Category	Antineoplastic Agent, Antimetabolite. ATC: L01XX05
Indications	**N.B.** *Refer to literature and specific protocols for all indications used.* • Resistant chronic myeloid leukemia. • Locally advanced squamous cell carcinomas of the head and neck, (excluding lip) in combination with concurrent chemoradiation. • The treatment of cancer of the cervix in conjunction with radiotherapy. • Essential thrombocythemia or polycythemia vera with high risk for thromboembolic complications.
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols.* **N.B.** Dosage should be based on the patient's actual or ideal weight, whichever is the less. Therapy should be monitored by repeat blood counts. N.B. Prophylactic administration of folic acid is recommended. • **Continuous therapy** - Chronic myeloid leukemia: 40 mg/kg daily, may be reduced to 20/kg if WBC <2,000/mm^3. The dose is then adjusted individually to keep the white cell count at 5–10 x 10^3/ mm^3. - Essential thrombocythemia: initial doses of 15 mg/kg/day with dose adjustment to maintain a platelet count below 600 x 10^9 /l without lowering the white blood cell count below 4 x 10^9 /l. - Polycythemia vera: initial dose: 15 – 20 mg/kg/day. Hydroxycarbamide dose should be adjusted individually to maintain the hematocrit below 45 % and platelet count below 400 x 10^9 /l. In most patients this can be achieved with hydroxycarbamide given continuously at average daily doses of 500 -1000 mg. • **Intermittent regimen** (suitable for cancer of the cervix): 80 mg/kg in single doses should be given every third day. Intermittent regimes are of diminished effect on the bone marrow, but if low counts are produced, omit 1 dose or more.
Dosage Adjustment	**N.B.** *Refer to protocol used for specific dose modifications.* **Dosing: Altered Kidney Function: Adult** CrCl ≥60 mL/minute: No dosage adjustment is necessary. CrCl <60 mL/minute: Initial: Administer 50% of the usual indication-specific dose; titrate based on tolerance and response. **Dosing: Hepatic Impairment: Adult**

	No adjustments are necessary.
Contra-indications	• Hypersensitivity to the active substance or to any of the excipients. • Marked leucopenia (<2.5 *10^9/L), thrombocytopenia (< 100x10^9/L), or severe anemia.
Adverse Drug Reactions	**Bone marrow suppression** **Cutaneous vasculitic toxicities** **Second primary malignancies** **>10%** **Dermatologic**: Eczema (infants and children: 13%), xeroderma (adults: 12%). **Hematologic and oncologic**: Macrocytosis (MCV >97: 42%), neutropenia (5% to 13%; severe neutropenia: ≤1%). **Infection**: Bacterial infection (children and adolescents: 16%; adults: 4%), infection (40% to 43%; serious infection: 4% to 18%). **Nervous system**: Headache (children and adolescents: 7%; adults: 20%; severe headache: 1% to 3%). **1% to 10%** **Cardiovascular**: Peripheral edema (adults: 3%). **Dermatologic**: Alopecia (adults: 5%), dermal ulcer (adults: 7%), dermatological reaction (children and adolescents: 4%), leg ulcer (7%). **Endocrine & metabolic**: Vitamin D deficiency (children and adolescents: 6%), weight gain (2% to 4%). **Gastrointestinal**: Acute mucocutaneous toxicity (5%), constipation (children and adolescents: 3%), diarrhea (adults: 3%), nausea (3% to 6%; severe nausea: <1%), upper abdominal pain (adults: 5%). Genitourinary: Disorder of urinary system (children and adolescents: ≤2%), urinary tract infection (adults: 4%). **Hematologic and oncologic**: Anemia (4% to 10%; severe anemia: 2% to 3%), thrombocytopenia (7%; severe thrombocytopenia: ≤1%). **Infection**: Influenza (adults: 4%); parvovirus B19 seroconversion (children and adolescents: 4%), viral infection (4% to 10%). **Nervous system**: Asthenia (adults: 9%), dizziness (adults: 9%), fatigue (adults: 5%), severe nervous system disease (4%). **Neuromuscular and skeletal**: Arthralgia (adults: 9%; severe arthralgia: <1%), back pain (adults: 5%), limb pain (adults: 3%). **Renal**: Renal disease (≤2%). **Respiratory**: Asthma (infants and children: 9%), bronchitis (adults: 4%), cough (adults: 6%), dyspnea (adults: 4%), nasopharyngitis (adults: 4%), pulmonary disease (adults: 5%). **Miscellaneous**: Fever (8%).
Monitoring Parameters	• CBC with differential, Platelet count at baseline and once weekly. • Kidney function test. • Liver function test.

Drug Interactions	***Risk X: Avoid combination*** Abrocitinib, Baricitinib, BCG (Intravesical), BCG Products, Betibeglogene Autotemcel, Brivudine, Cladribine, Dengue Tetravalent Vaccine (Live), Deucravacitinib, Didanosine, Dipyrone, Fexinidazole, Filgotinib, Mumps- Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Pimecrolimus, Poliovirus Vaccine (Live/Trivalent/Oral), Ritlecitinib, Ruxolitinib (Topical), Stavudine, Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Typhoid Vaccine, Upadacitinib, Vaccines (Live) Yellow Fever Vaccine. ***Risk D: Consider therapy modification*** Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), Deferiprone, Denosumab, Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating).
Pregnancy and Lactation	**Pregnancy**: Limited Human Data Suggest Low Risk. Fetal harm may occur theoretically. A careful follow-up with adequate clinical, biological and ultrasonographic examinations should be considered. **Lactation**: Not recommended due to potential for serious adverse reactions in infants.
Administration	**Hazardous agent** (NIOSH 2016 [group 1]): Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. **Administration: Oral** Administer at the same time each day. **N.B**. If the patient prefers, or is unable to swallow capsules, the contents of the capsule may be emptied into a glass of water and taken immediately. **N.B** Supplemental administration of folic acid is recommended; hydroxyurea may mask development of folic acid deficiency. **N.B**. Refer to manufacturer PIL for specific considerations.
Emetogenicity	**Minimal to low emetic risk** (<30% frequency of emesis).
Warnings/ Precautions	• **Myelosuppression:** Bone marrow suppression may occur, and leukopenia is generally its first and most common manifestation. If WBC falls below $2.5x10^9$/L or platelet count to (< $100x10^9$/L) therapy should be interrupted. Counts should be rechecked after 3 days and treatment resumed when they rise to normal levels. Recovery from myelosuppression is usually rapid when therapy is discontinued. • **Elderly** patients may be more sensitive to the effects of hydroxycarbamide and may require a lower dosage regimen. • **Macrocytosis** may occur, which is self-limiting, and is often seen early during treatment. The morphologic change resembles pernicious anemia but is not related to vitamin B12 or folic acid deficiency. This may mask the diagnosis of pernicious anemia. Prophylactic administration of folic acid is recommended.

	• **HIV patients**: is not licensed for use in combination with antiretroviral agents for HIV disease and it may cause treatment failure and toxicities (in some cases fatal) in HIV patients. • **Secondary malignancies:** Leukemia occurred in patients receiving long-term therapy for myeloproliferative disorders, such as polycythemia. Skin cancer has also been reported in patients receiving long-term hydroxyurea. Advise protection from sun exposure and monitor for the development of secondary malignancies. • **Vasculitic Toxicities:** Cutaneous vasculitic toxicities, including vasculitic ulcerations and gangrene, have occurred in patients with myeloproliferative disorders during therapy with hydroxyurea. These vasculitic toxicities were reported most often in patients with a history of, or currently receiving, interferon therapy. If cutaneous vasculitic ulcers occur, institute treatment and discontinue Hydroxyurea. • **Live Vaccinations:** Avoid use of live vaccine in patients taking Hydroxyurea for risk of severe infection. Patient's antibody response to vaccines may be decreased. Consider consultation with a specialist. • **Radiation Recall:** Patients who have received irradiation therapy in the past may have an exacerbation of post irradiation erythema. Monitor for skin erythema in patients who previously received radiation and manage symptomatically. • **Pulmonary Toxicity:** Interstitial lung disease including pulmonary fibrosis, lung infiltration, pneumonitis, and alveolitis/allergic alveolitis (including fatal cases) have been reported in patients treated for myeloproliferative neoplasm. Monitor patients developing pyrexia, cough, dyspnea, or other respiratory symptoms frequently, investigate and treat promptly. Discontinue Hydroxyurea and manage with corticosteroids.
Storage and Light Sensitivity	• Keep between 15°C and 30°C. • Protect from light and moisture. **N.B**. Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• Avoid bleeding and getting infected. Use sun protections. • This medication is carcinogenic. Wash your hands after handling hydroxyurea capsules or packaging. • Your doctor may tell you to drink plenty of liquids e.g., 8 cups a day, during the first one to two weeks of treatment. This helps prevent kidney problems. • Tell your doctor If you have any of these health problems: Anemia (other than sickle cell anemia) or wounds on the legs (leg ulcers), lung problems. • Follow your lab tests as told by your physician.

Retinoids

1. All-trans retinoid acid (ATRA)

Generic Name	Tretinoin (All trans Retinoic Acid)
Dosage Form/ Strengths	Capsule 10 mg
Route of Administration	Oral
Pharmacologic Category	Antineoplastic Agent, Retinoic Acid Derivative. ATC Code: L01XF01.
Indications	**N.B.** *Refer to literature and specific protocols for all indications*. **Acute promyelocytic leukemia** (newly diagnosed, relapsed or refractory to chemotherapy) in adults and pediatric patients from 1 year of age.
Dosage Regimen	***N.B.*** *Different doses and regimens have been used; consult the literature for specific protocols.* **Acute promyelocytic leukemia: Adult, pediatrics** • **Oral**: 45 mg/m^{2}daily in 2 equally divided doses. This is approximately 8 capsules per adult patient per day. • **For children**: May reduce dose to 25mg/m^2 daily to decrease related toxicity. • **Duration**: Discontinue 30 days after achievement of complete remission or after 90 days of treatment, whichever comes first.
Dosage Adjustment	**N.B.** *Refer to the protocol used for specific dose modifications.* **Altered Kidney Function: Adult and pediatric:** Limited data. Reduce dose to 25mg/m^2 as a precautionary measure. **Hepatic Impairment: Adult and pediatric** Limited data. Reduce dose to 25mg/m^2 as a precautionary measure.
Contra-indications	• Hypersensitivity to tretinoin, other retinoids, parabens, or any component of the formulation. • Combination with vitamin A, tetracyclines, retinoids. • Pregnancy and Breastfeeding.
Adverse Drug Reactions	**>10%** **Cardiovascular**: Cardiac arrhythmia (23%), chest discomfort (32%), edema (29%), flushing (23%), hypertension (11%), hypotension (14%), peripheral edema (52%), phlebitis (11%). **Dermatologic**: Alopecia (14%), diaphoresis (20%), pruritus (20%), skin changes (14%), skin rash (54%), xeroderma (≤77%). **Endocrine & metabolic**: Hypercholesterolemia (≤60%), hypertriglyceridemia (≤60%), weight gain (23%), weight loss (17%). **Gastrointestinal**: Abdominal distention (11%), abdominal pain (31%), anorexia (17%), constipation (17%), diarrhea (23%), dry mucous membranes (≤77%), dyspepsia (14%), gastrointestinal hemorrhage (34%), nausea (≤57%), stomatitis (26%), vomiting (≤57%).

Hematologic & **oncologic**: Differentiation syndrome (≤25%), disseminated intravascular coagulation (26%), hemorrhage (60%), leukocytosis (40%).
Hepatic: Increased liver enzymes (50% to 60%).
Infection: Infection (58%).
Nervous system: Anxiety (17%), confusion (11%), depression (14%), dizziness (20%), headache (86%), insomnia (14%), malaise (66%), pain (37%), paresthesia (17%), shivering (63%).
Neuromuscular & skeletal: Myalgia (14%), ostealgia (77%).
Ophthalmic: Eye disease (17%), visual disturbance (17%).
Otic: Otalgia (23%; including a feeling of ear fullness).
Renal: Renal insufficiency (11%).
Respiratory: Dyspnea (60%), pleural effusion (20%), pneumonia (14%), rales (14%), respiratory insufficiency (26%), upper respiratory system symptoms (63%), wheezing (expiratory: 14%).
Miscellaneous: Fever (83%).

1% to 10%

Cardiovascular: Acute myocardial infarction (3%), cardiomegaly (3%), cardiomyopathy (3%), heart failure (6%), heart murmur (3%), ischemia (3%), myocarditis (3%), pericarditis (3%).
Dermatologic: Cellulitis (8%), pallor (6%).
Endocrine & metabolic: Acidosis (3%), fluid volume disorder (6%).
Gastrointestinal: Gastrointestinal ulcer (3%).
Genitourinary: Benign prostatic hypertrophy (3%), dysuria (9%), urinary frequency (3%).
Hematologic & oncologic: Disorder of the lymphatic system (6%).
Hepatic: Ascites (3%), hepatitis (3%), hepatosplenomegaly (9%).
Hypersensitivity: Facial edema (6%).
Nervous system: Abnormal gait (3%), agitation (9%), agnosia (3%), aphasia (3%), asterixis (3%), ataxia (3%), brain edema (3%), central nervous system depression (3%), cerebellar disorder (3%), cerebral hemorrhage (9%), cerebrovascular accident (3%), coma (3%), dementia (3%), drowsiness (3%), dysarthria (3%), encephalopathy (3%), facial nerve paralysis (3%), forgetfulness (3%), hallucination (6%), hemiplegia (3%), hyporeflexia (3%), hypothermia (3%), intracranial hypertension (9%), loss of consciousness (3%), seizure (3%), speech disturbance (slowing: 3%), tremor (3%).
Neuromuscular & skeletal: Lower extremity weakness (3%), osteomyelitis (3%).
Ophthalmic: Decreased pupillary reflex (3%), decreased visual acuity (6%), visual field defect (3%).
Otic: Hearing loss (≤6%; may be irreversible).
Renal: Acute kidney injury (3%), flank pain (9%), renal tubular necrosis (3%).
Respiratory: Asthma (3%), laryngeal edema (3%), lower respiratory signs and symptoms (9%), pulmonary edema (3%), pulmonary hypertension (3%),

	pulmonary infiltrates (6%).
Monitoring Parameters	• Liver function tests at baseline and as clinically indicated. • Triglyceride and cholesterol levels at baseline and frequently during treatment. • CBC with differential and coagulation profile. • Serum creatinine. • ECG monitoring prior to and during therapy. • Monitor closely for signs of differentiation syndrome (e.g. monitor volume status, pulmonary status, temperature, respiratory functions). • Monitor for pregnancy before and during treatment.
Drug Interactions	***Risk X: Avoid combination*** Aminolevulinic Acid (Systemic), Bromperidol, Multivitamins/Fluoride (with ADEK, Folate, Iron), Multivitamins/Minerals, Tetracyclines, Vitamin A. ***Risk D: Consider therapy modification*** Amifostine, Antifibrinolytic Agents, Obinutuzumab, Progestins (Contraceptive).
Pregnancy and Lactation	**Pregnancy**: Avoid. Embryo-fetal loss and malformations may occur if Tretinoin is administered during pregnancy. Effective contraception method should be used during treatment and for 1 month after the last dose for females and for 1 week after the last dose for males. Tretinoin may impair male fertility. **Lactation**: No data. Breastfeeding must be discontinued due to the potential for serious adverse reactions. Advise women not to breastfed during treatment and for 1 week after the last dose.
Administration	**Administration: Oral** ○ Administer with a meal. ○ Swallow capsules whole with water. Do not chew, dissolve, or open capsule. Do not take a missed dose unless it is more than 10 hours until the next scheduled dose. If vomiting occurs after administration, do not take an additional dose, but continue with the next scheduled dose. **N.B.** Refer to manufacturer PIL for specific considerations.
Emetogenicity	Minimal or low (<30%).
Warnings/ Precautions	**Differentiation syndrome (DS)**: • About 25% of patients with acute promyelocytic leukemia (APL) treated with Tretinoin have experienced differentiation syndrome. • It is characterized by fever, dyspnea, acute respiratory distress, pulmonary infiltrates, hypotension, pleural and pericardial effusions, peripheral edema, weight gain, and may progress to pulmonary, hepatic, renal and multi-organ failure. DS is frequently associated with hyperleukocytosis. Fatalities due to multiorgan failure have occurred. • Differentiation syndrome generally occurs during the first month of treatment, with some cases reported following the first dose. • Early recognition and treatment of DS is of major importance. Treatment

with (IV 10 mg Dexamethasone every 12 hours for a minimum of 3 days or until resolution of the symptoms) must be initiated immediately for patients with early clinical signs of the syndrome. In cases of severe DS, temporary interruption of tretinoin therapy should be considered.

Cardiovascular effects:

- QTc prolongations have been observed in connection with combination therapy of tretinoin and arsenic trioxide. This might lead to life-threatening torsade de pointes arrhythmias.
- Venous thrombosis and myocardial infarction (MI) have been reported in patients without risk factors for thrombosis or MI. The risk for thrombosis (arterial and venous) is increased during the first month of treatment. Use with caution with antifibrinolytic agents; thrombotic complications have been reported (rarely) with concomitant use.

Leukocytosis:

- During treatment, about 40% of patients may develop rapidly evolving leukocytosis which is associated with a higher risk of life-threatening complications.
- Immediate treatment of patients with a white blood cell (WBC) count of ≥ 5 x 10^9 /L at diagnosis or at any time during therapy is recommended.
- Patients experiencing hyperleukocytosis should be treated with full-dose anthracycline-based chemotherapy.
- Consider use of Hydroxyurea for treatment of leukocytosis in patients treated with combination therapy of Tretinoin with Arsenic trioxide, to keep WBC < 10,000/µL.

Pseudotumor cerebri:

- Retinoids have been associated with pseudotumor cerebri (benign intracranial hypertension), especially in children. Concurrent use of other drugs associated with this effect (e.g., Tetracyclines) may increase risk. Early signs and symptoms include papilledema, headache, nausea, vomiting, visual disturbances, intracranial noises, or pulsate tinnitus.
- If intracranial hypertension/ Pseudotumor cerebri occurs, a reduction of Tretinoin dose is recommended in addition to administration of diuretics (acetazolamide), corticosteroids and/or analgesics.

Lipid effects: Up to 60% of patients experienced hypercholesterolemia or hypertriglyceridemia, which may be reversible upon completion of treatment.

Hepatotoxicity:

Elevated liver function test results may occur during treatment. Most liver function test abnormalities will resolve without interruption of treatment or after therapy completion.

Psychiatric disorders:

Depression, anxiety, and mood alterations have been reported in patients treated with systemic retinoids, including tretinoin. Monitor for signs.

CNS effects:

	Tretinoin has minor or moderate influence on the ability to drive and use machines, particularly if patients are experiencing dizziness or severe headache.
Storage and Light Sensitivity	Store between 15°C and 30°C. Keep away from light and moisture. **N.B.** Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• The risk of severe and fatal birth defects is very high if you take this drug at any time while pregnancy. Use 2 methods of contraception for 1 month before you start this drug, while you take it, and for 1 month after your last dose. • Tell you doctor If you are taking other medicines e.g. Tetracycline, any product that has vitamin A in it. • Have your blood work and other lab tests checked as you have been told by your doctor. • Call your doctor right away if you have signs of a blood clot like chest pain or pressure; coughing up blood; shortness of breath; swelling, warmth, numbness, change of color, or pain in a leg or arm; or trouble speaking or swallowing. Also, if a bad headache, dizziness, throwing up, change in eyesight, change in hearing or seizures occurred call your doctor right away.
Pharmaco-genomics	• Acute promyelocytic leukemia (APL) is characterized by the presence of the t (15;17) translocation or *PML-RARA* gene expression. Tretinoin is not recommended for use in patients without t (15;17) translocation. Testing is recommended.

Supportive Medicines

A. Erythropoiesis-Stimulating Agent

1. Epoetin Alfa

Generic Name	Epoetin Alfa
Dosage Form /Strengths	**Solution for injection in Pre-filled Syringe:** 2000 I.U./ml, 2000 I.U/0.5ml, 4000 I.U./0.4ml, 10000 I.U./ml, 40000 I.U./ml.
Route of Administration	*SC, IV*
Pharmacologic Category	Erythropoiesis-Stimulating Agent (ESA); Hematopoietic Agent. **ATC:** B03XA01
Indications	**N.B.** *Refer to literature and specific protocols for all indications*. • Treatment of anemia due to: ○ Chronic Kidney Disease (CKD) in patients on dialysis and not on dialysis (hemoglobin ≤10 g/dL). ○ Zidovudine in patients with HIV-infection. ○ Myelosuppressive chemotherapy, upon initiation if the hemoglobin is less than 10 g/dL and if there is a minimum of two additional months of planned chemotherapy or for patient at risk of transfusion as assessed by the patient's general status (e.g. cardiovascular status, pre-existing anemia at the start of chemotherapy). • Reduction of allogeneic RBC transfusions in patients undergoing elective, noncardiac, nonvascular surgery. • In a predonation programme to increase the yield of autologous blood. (In adult patients with moderate anemia (hemoglobin: 10-13 g/dL, with no iron deficiency). • Treatment of symptomatic anemia (hemoglobin ≤10 g/dL) in adults with low- or intermediate-1-risk primary myelodysplastic syndromes (MDS) who have low serum erythropoietin (<200mU/ml).
Dosage Regimen	***N.B.*** *Different doses and regimens have been used; consult the literature for specific protocols.* N.B. Do not increase the dose more frequently than once every 4 weeks. • **Patients with CKD**: ○ *Initial dose:* Adult: **IV or SC:** 50 to 100 Units/kg 3 times weekly. Pediatrics: **IV or SC**: 50 Units/kg 3 times weekly. ○ *Maintenance dose* should be individualized. Patients should be monitored closely to ensure that the lowest effective dose is used to give adequate effect. Increments of 25 IU/kg are used.

- *Maximum dose*: 150 IU/kg, 3 times per week or 240 IU/kg (up to a maximum of 20,000 IU) once weekly.
- Reduce or interrupt the dose, If the hemoglobin level approaches or exceeds 10 g/dL in adults or 12 g/dL in children.
- **Patients on dialysis**:
  - *Initial*: **IV**: 50 IU/kg, 3 times per week. increase or decrease the dose by 25 IU/kg (3 times per week) until the desired hemoglobin concentration.
  - *Maintenance phase***:** Total weekly dose is between 75 IU/kg and 300 IU/kg.
- **Peritoneal dialysis**:
  - *Initial* **IV**: 50 IU/kg, 2 times per week.
  - *Maintenance phase*: between 25 IU/kg and 50 IU/kg, 2 times per week in 2 equal injections.

• **Patients on Zidovudine due to HIV-infection**:

IV or SC: 100 Units/kg 3 times weekly. Dose increase by 50 - 100 Units/kg at 4-8-week intervals is needed if Hb not increased in 8 weeks treatment.

• **Patients with Cancer on Chemotherapy**:

- Adults: **SC**: 150 IU/kg 3 times weekly or 450 IU/kg once or 40,000 IU weekly.
- Pediatrics ≥ 5 years: **IV**: 600 Units/kg weekly.
- Adjust dose to maintain Hb levels between 10-12g/dL.
- Reduce dose by 25% if: Hemoglobin increases greater than 1 g/dL in any 2-week period or hemoglobin reaches a level needed to avoid RBC transfusion.
- Withhold dose if hemoglobin exceeds a level needed to avoid RBC transfusion. Reinitiate at a dose 25% below the previous dose when hemoglobin approaches a level where RBC transfusions may be required.
- Increase dose after 4 weeks if no adequate effect to 300 Units/kg 3 times weekly **OR** 60,000 Units weekly in adults **OR** 900 Units/kg (maximum 60,000 Units) weekly in pediatric patients.
- Discontinue after 8 weeks if no adequate response.

• **Surgery Patients**:

SC: 300 Units/kg daily for 15 days, 10 days before surgery, on day of surgery, and for 4 days after surgery **OR** 600 Units/kg weekly in 4 doses administered 21, 14, and 7 days before surgery and on the day of surgery.

• **Treatment of adult surgery patients in an autologous predonation programme:**

IV: 600 IU/kg, 2 times per week for 3 weeks prior to surgery in mildly anemic patients after completion of the blood donation procedure.

• **Treatment of adult patients with low- or intermediate-1-risk MDS**

- Initial: SC: 450 IU/kg weekly in patients with symptomatic anemia (maximum total dose is 40,000 IU).

	○ Appropriate dose adjustments should be made to maintain hemoglobin concentrations. Dose should not be increased over the maximum of 1050 IU/kg (total dose 80,000 IU) per week.
Dosage Adjustment	**N.B.** *Refer to the protocol used for specific dose modifications.* • **Altered Kidney Function:** No dosage adjustment necessary for any degree of kidney impairment. • **Altered hepatic Function** No dose adjustment available. Caution in chronic liver failure. Safety of Epoetin Alfa has not been established in patients with hepatic dysfunction.
Contra-indications	• Serious allergic reactions to Epoetin Alfa products or any component of the formulation. • Uncontrolled hypertension. • Pure red cell aplasia (PRCA) that begins after treatment with Epoetin Alfa or other Epoetin protein drugs. • Surgery patients who for any reason cannot receive adequate antithrombotic prophylaxis.
Adverse Drug Reactions	**>10%** **Cardiovascular:** Hypertension (6% to 28%) **Central nervous system:** Headache (5% to 18%) **Dermatologic:** Pruritus (16% to 21%), skin rash (2% to 19%) **Gastrointestinal:** Nausea (35% to 56%), vomiting (19% to 28%) **Local:** Injection site pain (9% to 13%) **Neuromuscular & skeletal:** Arthralgia (10% to 16%) **Respiratory:** Cough (4% to 26%) **Miscellaneous:** Fever (10% to 42%) **1% to 10%** **Cardiovascular:** Thrombosis of hemodialysis vascular access (8%), thrombosis (≤6%), deep vein thrombosis (5% to 6%), edema (3%) **Central nervous system:** Dizziness (10%), chills (4% to 7%), insomnia (6%), depression (5%) **Dermatologic:** Urticaria (3%) **Endocrine & metabolic:** Weight loss (9%), hyperglycemia (6%), hypokalemia (5%) **Gastrointestinal:** Stomatitis (10%), dysphagia (5%) **Hematologic & oncologic:** Leukopenia (8%) **Local:** Irritation at injection site (7%) **Neuromuscular & skeletal:** Myalgia (10%), muscle spasm (7%), ostealgia (7%) **Respiratory:** Upper respiratory tract infection (7%)

Monitoring Parameters	• Evaluate iron status in all patients before and during treatment. Administer supplemental iron when serum ferritin is less than 100 mcg/L or when serum transferrin saturation is less than 20%. • Hemoglobin (before, after initiation and following dose adjustments). • Platelets regularly during the first 8 weeks of therapy. • Serum electrolytes should be monitored in chronic renal failure patients. • Blood Pressure • Monitor for signs of skin reactions and seizures. **Diabetes:** HbA_{1c} is not useful as a glycemic indicator in patients treated with an ESA as may artificially lower HbA1c. Other monitoring parameters may be more useful.
Drug Interactions	***Risk X: Avoid combination*** Lovotibeglogene Autotemcel, Roxadustat, Vadadustat.
Pregnancy and Lactation	**Pregnancy:** No or limited data. Studies in animals have shown reproductive toxicity. Use in pregnancy only if the potential benefit outweighs the potential risk to the fetus. **Breastfeeding Considerations** Endogenous erythropoietin is found in breast milk. Caution should be exercised when administered to a lactating woman.
Administration	**Preparation and Administration** **IV**: Do not shake. Do not dilute. May dilute with bacteriostatic 0.9% sodium chloride injection in a 1:1 ratio using aseptic technique at the time of administration. **Administration: Intravenous** Administer over at least 1-5 minutes, depending on the total dose. A slower administration is preferable in patients who react to the treatment with "flu-like" symptoms **Administration: Subcutaneous** • A maximum volume of 1 mL at one injection site should generally not be exceeded. In case of larger volumes, more than one site should be chosen for the injection. • The injections should be given in the limbs or the anterior abdominal wall. Rotate injection site. **N.B.** Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	• **Traceability of the biological product**: The name and the batch number of the administered product should be clearly recorded. • **Hypertension**: Monitor closely. Caution in presence of untreated, inadequately controlled hypertension. Hypertensive crisis with encephalopathy and seizures have occurred even in normal blood pressure or hypotensive patients. • **Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism**:

	Using Epoetin Alfa to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit. Use caution in patients with coexistent cardiovascular disease and stroke or risk factors. • **Seizures**: Epogen increases the risk for seizures in patients with CKD. Increase monitoring of these patients for changes in seizure frequency or premonitory symptoms. • **Before Initiation and during therapy**: Correct or exclude other causes of anemia (e.g., iron, folate or Vitamin B12 deficiency, aluminium intoxication, infection or inflammation, blood loss, haemolysis and bone marrow fibrosis of any origin). • **Severe cutaneous adverse reactions:** Including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported in association with Epoetin treatment. If developed, withdraw immediately and an alternative treatment considered. • **Pure Red Cell Aplasia:** Antibody-mediated pure red cell aplasia (PRCA) has been reported after months to years of epoetin alfa treatment. If severe anemia and low reticulocyte count develop, withhold and evaluate for PRCA. • **Chronic renal failure patients:** When used for treatment of symptomatic anaemia in adult and paediatric, rate of increase in haemoglobin should be approximately 1 g/dL per month and should not exceed 2 g/dL per month to minimize risks of an increase in hypertension. • **Hyperkalaemia**: Serum electrolytes should be monitored in chronic renal failure patients. If an elevated or rising serum potassium level is detected, treat appropriately and consider ceasation of Epoetin Alfa until the serum potassium level has been corrected. • **Major elective orthopaedic surgery patients**: should receive adequate antithrombotic prophylaxis, as thrombotic and vascular events may occur in surgical patients, especially in those with underlying cardiovascular disease.
Storage and Light Sensitivity	• Store intact vials between (2°C to 8°C). Do not freeze. Do not shake. Do not freeze. • Protect from light. **N.B**. Refer to manufacturer PIL if there are specific considerations.
Patient Counselling Keys	• Tell your doctor about any health issues before administration. • Tell your doctor if any side effects developed during therapy. • Get your laboratory tests done ad directed by physician.

B. Granulocyte-colony stimulating factors

1. Filgrastim

Generic Name	Filgrastim
Dosage Forms/ Strengths	• Solution for injection/Infusion: 300 mcg/0.5ml, 300 mcg/1ml, 480 mcg/0.5ml. • Concentrate solution for infusion: 0.6 mg/ml. • Lyophilized Powder: 300 mcg/ml.
Route of Administration	SC, IV
Pharmacologic Category	Colony Stimulating Factor; Hematopoietic Agent ATC: L03AA02
Indications	• **In patients treated with chemotherapy for malignancy** (except chronic myeloid leukemia and myelodysplastic syndromes) for reduction in the duration of neutropenia and the incidence of febrile neutropenia • **In patients acutely exposed to myelosuppressive doses of radiation** to increase survival. • **In patients undergoing myeloablative therapy followed by bone marrow transplantation** (at high risk of prolonged severe neutropenia) for reduction in the duration and clinical sequelae of neutropenia. • **In symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia** to reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers)**.** • **In patients with advanced HIV infection,** for treatment of persistent neutropenia (ANC≤ 1.0×10^9 /l) when other options to manage neutropenia are inappropriate**.** • **Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis**.
Dosage Regimen	• **With myelosuppressive chemotherapy**: **SC**: 5 mcg/kg/day **OR** 230 mcg/m^2/day. **IV:** 5mcg/kg/day as short IV infusion (15 - 30 minutes) or continuous IV infusion. The first dose of Filgrastim should be administered after starting cytotoxic chemotherapy with at least 24 hours. • **Patients acutely exposed to myelosuppressive doses of radiation**: **SC**: 10mcg/kg/day. Continue administration of until ANC remains > 1,000/mm^3 for 3 consecutive CBCs (CBC approximately made every third day) or exceeds 10,000/mm^3 after a radiation-induced nadir. • **With myeloablative therapy followed by bone marrow transplantation**: **IV**: 10mcg/kg/day as IV infusion (30 minutes) or 24hour infusion. The first dose should be administered at least after bone marrow infusion. Reduce dose to 5mcg/kg/day if ANC remains > 1.0×10^9/l for 3 consecutive days and discontinue after 3 more consecutive days. Increase dose if ANC decreased to < 1.0×10^9/l.

	• **Patients with congenital neutropenia**: **SC**: initial: 12 mcg/kg/day, as a single dose or in divided doses. **Patients with cyclic or idiopathic neutropenia**: **SC**: initial: 5mcg/kg/day, as a single dose or in divided doses. After one to two weeks of therapy, the initial dose may be doubled or halved depending upon the patient's response. Subsequently the dose may be individually adjusted every 1 to 2 weeks to maintain the average neutrophil count between 1.5-10 × 10^9/l. • **In patients with HIV infection:** **SC**: 1mcg/kg/day, with titration up to a maximum of 4mcg/kg/day until a normal neutrophil count is reached. After reversal of neutropenia has been achieved 300mcg/day dose is recommended. Then adjust to minimal effective dose to maintain a normal neutrophil count. • **Patients undergoing autologous peripheral blood progenitor cell collection and therapy:** **SC**: 10mcg/kg/day, administer for at least 4 consecutive days before first leukapheresis procedure and continue until last leukapheresis. Optimally given for 6 to 7 days with leukaphereses on days 5, 6, and 7. **Pediatric dosing**: Same as adult dosing.
Dosage Adjustment	• **Altered Hepatic Function.** No dose adjustment needed. • **Altered Kidney Function.** No dose adjustment needed. **In case of Glomerulonephritis due to Filgrastim:** Consider dose reduction or treatment interruption.
Contra-indications	Hypersensitivity to the active substance or to any of the excipients.
Adverse Drug Reactions	**>10%** **Cardiovascular**: Chest pain (13%) **Dermatologic**: Skin rash (14%) **Gastrointestinal**: Nausea (43%) **Hematologic & oncologic**: Thrombocytopenia (infants, children, adolescents, and adults: 34% to 38%) **Hepatic**: Increased serum alkaline phosphatase (6% to 11%) **Nervous system**: Dizziness (14%), fatigue (20%), pain (12%) **Neuromuscular & skeletal**: Back pain (15%), ostealgia (3% to 30%) **Respiratory**: Cough (14%), dyspnea (13%) **Miscellaneous**: Fever (infants, children, adolescents, and adults: 8% to 48%) **1% to 10%** **Cardiovascular**: Hypertension (≥5%). **Dermatologic**: Alopecia (≥5%), erythema of skin (≥2%), maculopapular rash (≥2%).

	Endocrine & metabolic: Increased lactate dehydrogenase (6%). **Gastrointestinal**: Diarrhea (infants, children, adolescents, and adults: 6%). **Genitourinary**: Urinary tract infection (≥5%). **Hematologic & oncologic**: Anemia (≥5%), leukocytosis (≤2%), splenomegaly (≥5%). **Hypersensitivity**: Hypersensitivity reaction (≥5%; including severe hypersensitivity reactions). **Immunologic:** Antibody development (infants, children, adolescents, and adults: 1% to 3%; no evidence of neutralizing response). **Infection**: Sepsis (≥5%). **Nervous system**: Headache (infants, children, adolescents, and adults: 6% to 10%), hypoesthesia (≥5%), insomnia (≥5%). **Neuromuscular & skeletal**: Arthralgia (9%), limb pain (infants, children, adolescents, and adults: 6% to 7%), muscle spasm (≥5%), musculoskeletal pain (≥5%). **Respiratory:** Bronchitis (≥5%), epistaxis (≥2%), upper respiratory tract infection (≥5%).
Monitoring Parameters	• CBC with differential • Platelet count
Drug Interactions	***Risk X: Avoid combination:*** Betibeglogene Autotemcel, Exagamglogene Autotemcel, Lovotibeglogene Autotemcel, Tisagenlecleucel ***Risk D: Consider therapy modification*:** Belotecan, Bleomycin, Topotecan
Pregnancy and Lactation	• **Pregnancy:** Not recommended. No adequate human data. No major differences were seen between treated and untreated women with respect to pregnancy outcome and newborn complications in small studies. Not recommended during pregnancy. • **Lactation**: No adequate data. A risk to the newborns/infants cannot be excluded.
Administration	**Preparation of administration:** Allow product to reach room temperature prior to use; after removal from refrigerator wait a minimum of 30 minutes; discard after out of the refrigerator >24 hours. Make sure the medicine is clear and colorless. **IV:** Filgrastim should be diluted in 5% glucose solution to a final concentration NOT less than 5 mcg/mL. Do not dilute with saline at any time because the product may precipitate. Only clear solutions without particles should be used. Filgrastim diluted to concentrations from 5 mcg/mL to 15 mcg/mL should be protected from adsorption to plastic materials by the addition of Albumin (Human) to a final concentration of 2 mg/mL. **Administration: IV** Administered IV as a short infusion over 15 to 30 minutes or by continuous infusion or as an infusion of no longer than 24 hours according to indication. Not administered earlier than 24 hours after cytotoxic chemotherapy.

	Administration: Subcutaneous Inject Filgrastim in the outer area of upper arms, abdomen, thighs, or upper outer areas of the buttock. Rotate injection site; do not inject into areas that are tender, red, bruised, hardened, scaly, or scarred, or sites with stretch marks. Do not administer earlier than 24 hours after or in the 24 hours prior to cytotoxic chemotherapy. **N.B** Refer to manufacturer PIL if there are specific considerations
Warnings/ Precautions	• **Traceability of the biological product**: The name and the batch number of the administered product should be clearly recorded. • **Fatal splenic rupture**: Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture. May be asymptomatic and can be fatal. Therefore, spleen size should be carefully monitored (e.g. clinical examination, ultrasound). • **Pulmonary adverse effects**: Evaluate patients who develop cough, fever and dyspnea and radiological lung infiltrates or respiratory distress for acute respiratory distress syndrome (ARDS). Discontinue Filgrastim in patients with ARDS and appropriate treatment should be given. • **Serious allergic reactions, including anaphylaxis**: Permanently discontinue Filgrastim in patients with serious allergic reactions. • **Fatal sickle cell crises**: Caution in in patients with sickle cell trait or sickle cell disease. Discontinue Filgrastim if sickle cell crisis occurs. • **Glomerulonephritis**: Evaluate and consider dose-reduction or interruption of Filgrastim if developed. Urinalysis monitoring is recommended. • **Myelodysplastic syndrome or Chronic myeloid leukemia:** The safety and efficacy of Filgrastim administration in patients with myelodysplastic syndrome, or chronic myelogenous leukemia have not been established**.** • **Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML):** Monitor patients with breast and lung cancer using Filgrastim in conjunction with chemotherapy and/or radiotherapy for signs and symptoms of MDS/AML. • **Malignant cell growth**: Granulocyte colony-stimulating factor can promote growth of myeloid cells and some non-myeloid cells in vitro. • **Thrombocytopenia**: Monitor platelet counts. Reduce dose or temporary discontinue if thrombocytopenia developed (platelet count < 100×10^9 /L). • **Capillary leak syndrome**: Has been reported after granulocyte-colony-stimulating factor administration. Can be life-threatening if treatment is delayed. It is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. • **Aortitis**: Reported after G-CSF administration. Symptoms include fever, abdominal pain, malaise, back pain and increased inflammatory markers. In most cases aortitis was diagnosed by CT scan and generally resolved after withdrawal of G-CSF. • **Osteoporosis**: Monitoring of bone density may be needed in patients with underlying osteoporotic bone diseases who undergo continuous therapy with

	Filgrastim for more than 6 months.
Storage and Light Sensitivity	Store between (2°C to 8°C). Do not freeze. Protect from light and direct sunlight. Do not shake. **N.B** Refer to manufacturer PIL if there are specific considerations
Patient Counselling Keys	• Tell your doctor about any health issues before administration. • Tell your doctor if any side effects developed during therapy. • Get your laboratory tests done ad directed by physician.

2. PegFilgrastim

Generic Name	Pegfilgrastim
Dosage Forms/ Strengths	Solution for injection in pre-filled syringes: 6mg/ 0.6ml
Route of Administration	SC
Pharmacologic Category	Colony Stimulating Factor; Hematopoietic Agent ATC code: L03AA13
Indications	Reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukemia and myelodysplastic syndromes)
Dosage Regimen	**Adult dosing** **SC**: 6 mg dose (a single pre-filled syringe) is recommended for each chemotherapy cycle, given at least 24 hours after cytotoxic chemotherapy. **Pediatric dosing** The safety and efficacy in children and adolescents (<45kg) have not yet been established. No overall differences in safety were identified between adult and pediatric patients based on post marketing data and scientific literature.
Dosage Adjustment	**Dosing: Altered Kidney Function: Adult** No dose adjustments needed in any degree of kidney impairment. **Dosing: Hepatic Impairment: Adult** No dose adjustments available. Not studied.
Contra-indications	Hypersensitivity to the active substance or to any of the excipients
Adverse Drug Reactions	**>10%** **Neuromuscular and skeletal**: Ostealgia (31%). **1% to 10%** **Neuromuscular and skeletal**: Limb pain (9%). **Postmarketing** **Cardiovascular**: Capillary leak syndrome, hypersensitivity angiitis, vasculitis (aortitis). **Dermatologic**: Sweet's syndrome **Hematologic and oncologic**: Sickle cell crisis, splenic rupture, splenomegaly, thrombocytopenia. **Hypersensitivity**: Anaphylaxis, severe hypersensitivity reaction. **Local**: Injection site reaction. **Renal**: Glomerulonephritis. **Respiratory**: Acute respiratory distress syndrome, pulmonary alveolar hemorrhage.
Monitoring Parameters	• CBC • Platelets

Drug Interactions	***Risk X: Avoid combination*** Betibeglogene Autotemcel, Exagamglogene Autotemcel, Lovotibeglogene Autotemcel, Tisagenlecleucel ***Risk D: Consider therapy modification*** Belotecan Bleomycin Topotecan
Pregnancy and Lactation	**Pregnancy**: No adequate human data. Potential risk. **Lactation**: There is insufficient data. A risk to the newborns or infants cannot be excluded**.**
Administration	**Subcutaneous Administration**: The injections should be given subcutaneously into the thigh, abdomen or upper arm. **N.B.** Refer to manufacturer PIL for specific considerations.
Warnings/ Precautions	• **Traceability of the biological product**: The name and the batch number of the administered product should be clearly recorded. • **Fatal splenic rupture**: Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture. May be asymptomatic and can be fatal. Therefore, spleen size should be carefully monitored (e.g. clinical examination, ultrasound). • **Pulmonary adverse effects**: Evaluate patients who develop cough, fever and dyspnea and radiological lung infiltrates or respiratory distress for acute respiratory distress syndrome (ARDS). Discontinue Pegfilgrastim in patients with ARDS and appropriate treatment should be given. • **Serious allergic reactions, including anaphylaxis**: Permanently discontinue Filgrastim in patients with serious allergic reactions. • **Fatal sickle cell crises**: Caution in in patients with sickle cell trait or sickle cell disease. Discontinue Filgrastim if sickle cell crisis occurs. • **Glomerulonephritis**: Evaluate and consider dose-reduction or interruption of Pegfilgrastim if developed. Urinalysis monitoring is recommended. • **Myelodysplastic syndrome or Chronic myeloid leukemia:** The safety and efficacy of Pegfilgrastim administration in patients with myelodysplastic syndrome, or chronic myelogenous leukemia have not been established**.** • **Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML):** Monitor patients with breast and lung cancer using Pegfilgrastim in conjunction with chemotherapy and/or radiotherapy for signs and symptoms of MDS/AML. • **Malignant cell growth**: Granulocyte colony-stimulating factor can promote growth of myeloid cells and some non-myeloid cells in vitro. • **Thrombocytopenia**: Regular monitoring of platelet count and hematocrit is recommended. • **Capillary leak syndrome**: Has been reported after granulocyte-colony-stimulating factor administration. Can be life-threatening if treatment is delayed. It is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration.

	• **Stevens-Johnson syndrome (SJS)**: Reported rarely with Pegfilgrastim and can be life-threatening or fatal. Discontinue permanently if the patient has developed SJS with the use of Pegfilgrastim. • **Aortitis**: Reported after G-CSF administration. Symptoms include fever, abdominal pain, malaise, back pain and increased inflammatory markers. In most cases aortitis was diagnosed by CT scan and generally resolved after withdrawal of G-CSF. • The safety and efficacy of Pegfilgrastim for the mobilization of blood progenitor cells in patients or healthy donors has not been adequately evaluated.
Storage and Light sensitivity	• Store between 2°C and 8°C. Do not freeze. Protect from light. Do not shake. • If left more than definite time in room temperature, it should be discarded. Refer to manufacturer label. • Throw away if have been frozen for more than one time. **N.B.** Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• Tell your doctor about any health issues before administration. • Tell your doctor if any side effects developed during therapy. • Get your laboratory tests done ad directed by physician.

C. Other supportive medicines

1. Calcium folinate

Generic Name	Calcium folinate (Calcium Leucovorin)
Dosage Forms/ Strengths	Solution for injection: 10 mg/ml (10ml, 20ml, 50ml, 100ml).
Route of Administration	IV, IM
Pharmacologic Category	Antidote; Chemotherapy Modulating Agent. ATC code: V03AF03
Indications	**N.B.** *Refer to literature and specific protocols for all indications.* • To diminish the toxicity and counteract effects, and after high doses of Methotrexate in cytotoxic therapy "Calcium Folinate Rescue" and overdose in adults and children. • Colorectal cancer, advanced or metastatic, in combination with Fluorouracil. • Treatment of megaloblastic anemias due to folic acid deficiency when oral therapy is not feasible. **N.B**. Calcium Folinate Injection is not indicated for use in the treatment of folic acid deficiency.
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols.* **Calcium Folinate Rescue with Methotrexate therapy:** **Notes**: Methotrexate monitoring is mandatory until not detected. Subsequent Calcium Folinate rescue doses and intervals depend on Methotrexate levels. **IV, IM**: The first dose is 15 mg (6-12 mg/m²) to be given 12-24 hours after starting Methotrexate infusion. The same dose is given every 6 hours throughout a period of 72 hours. May resume with oral forms. Additional Calcium folinate to be administered every 6 hours for 48 hours or until levels of Methotrexate are lower than 0.05µmol/l: - > 0.5 µmol/l: Administer 15 mg/m² - > 1.0 µmol/l: Administer 100 mg/m² - > 2.0 µmol/l: Administer 200 mg/m² **N.B.** Calcium Folinate Rescue is necessary with Methotrexate doses exceeding 500 mg/m² and should be considered with doses of 100 mg - 500 mg/m². **Colorectal cancer, advanced or metastatic, in combination with Fluorouracil:** ***Bimonthly regimen***: **IV infusion:** 200mg/m² (over two hours), followed by an IV bolus of 400 mg/m² of 5-Fluorouracil and a 22-hour IV infusion of 5-Fluorouracil (600 mg/m²) for 2 consecutive days, every 2 weeks on days 1 and 2.

	Weekly regimen: **IV Bolus** 20mg/m² or **IV infusion** 200 to 500 mg/m² over a period of 2 hours, plus 500 mg/m² 5-Fluorouracil as an IV bolus injection in the middle, or at the end, of the calcium folinate infusion. ***Monthly regimen:*** **IV Bolus** 20 mg/m² or **IV infusion** 200 to 500 mg/m² over 2 hours immediately followed by 425 or 370 mg/m² 5-Fluorouracil as an IV bolus injection over five consecutive days. **Megaloblastic Anemia Due to Folic Acid Deficiency:** IM, IV: Up to 1 mg daily
Dosage Adjustment	**N.B.** Refer to protocol used for specific dose modifications. • **Dosing: Altered Kidney Function:** No dose adjustments required. Caution • **Dosage in hepatic failure:** No adjustment required.
Contra-indications	• Hypersensitivity to the active substance or to any of the excipients. • Pernicious anemia or other anemias due to vitamin B12 deficiency.
Adverse Drug Reactions	**>10%** **Central nervous system:** Fatigue (≤13%), lethargy (≤13%), malaise (≤13%) **Dermatologic**: Alopecia (42% to 43%), dermatitis (21% to 25%) **Gastrointestinal**: Stomatitis (75% to 84%; grades ≥3: 27% to 29%), nausea (74% to 80%), diarrhea (66% to 67%), vomiting (44% to 46%), anorexia (14% to 22%) **Miscellaneous**: Drug toxicity **1% to 10%** **Gastrointestinal**: Constipation (3% to 4%) **Infection**: Infection (3% to 8%) **Frequency not defined**: Gastrointestinal: Gastrointestinal toxicity.
Monitoring Parameters	• Renal function. • Electrolytes. • Plasma Methotrexate concentration in high-dose therapy. Leucovorin is continued until the plasma methotrexate level <0.05 micromolar. • Assess for GI toxicity and seizures. • Calcium levels in patients receiving combined 5- Fluorouracil/Calcium Folinate treatment. (Calcium supplements may be needed).
Drug Interactions	***Risk X: Avoid combination:*** Trimethoprim: Calcium Folinate may diminish the therapeutic effect of Trimethoprim. ***Risk D: Consider therapy modification:*** Glucarpidase: Avoid leucovorin administration within 2 hours of Glucarpidase dosing).

Pregnancy and Lactation	**Pregnancy:** No adequate human data. Calcium Folinate Injection should be given to a pregnant woman only if the need is clearly demonstrated and the benefits have been weighed against the possible risks. **Lactation**: No human data. Calcium folinate can be used during breast-feeding when considered necessary.
Administration	**Route of administration**: Calcium Folinate Injection is used for intravenous or intramuscular injection. Do not administer intrathecally. **Preparation of administration:** **For IV infusion**: Dilute with 0.9% sodium chloride solution or 5% glucose solution. **Administeration**: - **IM administration**: Rotate sites of administration. - **IV infusion**: Rate should be < 160 mg/minute because of the calcium content. **N.B.** Refer to manufacturer PIL for specific considerations.
Emetogenicity	Non-emetogenic
Warnings/ Precautions	• **Route of administration**: Leucovorin Calcium should only be given by intramuscular or intravenous injection. It must not be administered intrathecally (fatal). • **GIT toxicity**: Patients receiving any combination therapy regimen involving Leucovorin and Fluorouracil should be carefully monitored for diarrhea and/or stomatitis/mucositis as these are the first indications that severe and potentially life-threatening toxicity could develop. • **Pernicious anemia:** Calcium folinate treatment may mask pernicious anemia and other anemias resulting from vitamin B12 deficiency. • **Anti-epileptics interactions**: Leucovorin may diminish the effect of anti-epileptic substances such as phenobarbital, primidone and phenytoin. During leucovorin administration in epileptic patients treated with these substances, there is a risk to increase the frequency of seizures due to a decrease of plasma concentrations of anti-epileptic drugs. • **Trimethoprim interactions**: The concomitant use with Trimethoprim-Sulfamethoxazole for the acute treatment of Pneumocystis jiroveci pneumonia in patients with HIV infection was associated with increased rates of treatment failure and morbidity. • Leucovorin Calcium Injection should only be used with 5-Fluorouracil or Methotrexate under the direct supervision of a clinician experienced in the use of cancer chemotherapeutic agents.
Storage and Light Sensitivity	• Injection: Store in refrigerator 2° to 8°C, Protect from light. • After dilution: may be kept for 3 days in room temperature. **N.B.** Refer to manufacturer PIL for specific considerations.
Patient Counselling	• Tell your doctor if you experience Signs of an allergic reaction. • If this drug is used with Fluorouracil, side effects from Fluorouracil may be

Keys	
	increased. Problems like diarrhea, mouth irritation, and mouth sores may happen more often, may be worse, and may last longer. If you have questions, talk with the doctor directly. • Tell your doctor if you are taking any antiseizures medications before taking ca leucovorin as it decreases these medications concentration in the plasma, therefore you may experience seizures or may worsen the effects.

2. Mesna

Generic Name	Mesna
Dosage Forms/ Strengths	• Solution for injection: 200mg/2ml, 400 mg/4ml. • Solution for I.V Infusion/ Injection or oral use: 400 mg/4ml.
Route of Administration	IV, Oral.
Pharmacologic Category	Antidote; Chemoprotective Agent. **ATC Code:** V03AF01
Indications	**N.B.** Refer to literature and specific protocols for all indications. Cytoprotective agent as a prophylactic agent against Oxazaphosphorine (Ifosfamide or Cyclophosphamide)-induced hemorrhagic cystitis in doses considered to be urotoxic.
Dosage Regimen	**N.B.** Different doses and regimens have been used; consult the literature for specific protocols. **IV dosing:** • **With IV bolus Ifosfamide or Cyclophosphamide or with oral Cyclophosphamide**: *IV infusion*: 20% weight by weight (w/w) of the dose of Ifosfamide or Cyclophosphamide at (0, 4, 8 hours) over 15-30 minutes. Total Mesna dose is 60% (w/w). • **In patients whose urothelium may be damaged from previous treatment with Ifosfamide or Cyclophosphamide or pelvic irradiation, or in patients who are not adequately protected by the standard dose of Mesna:** *IV*: 40% (w/w) of Ifosfamide or Cyclophosphamide dose given at (0, 3, 6 and 9 hours). (Total dose = 160% (w/w) of the Oxazaphosphorine dose). • **Where Ifosfamide is used as a 24-hour infusion:** - *Initial IV bolus* 20% (w/w) of the total Ifosfamide dose. - Followed by an *infusion* of 100% (w/w) of the Ifosfamide dose over 24 hours. - Then a further 12-hour *infusion* of 60% (w/w) of the Ifosfamide dose. - Total Mesna dose = 180% of the Ifosfamide dose. - The final 12-hour infusion of Mesna, after long-term or 24-hour infusion of Ifosfamide, may be replaced by boluses at 28, 32 and 36 hours, each of 20% (w/w) of the Ifosfamide dose, or by oral Mesna. **Oral dosing**: • **Oral use of Mesna ampoules with intermittent Oxazaphosphorine therapy:** - Initial IV injection: 20% (w/w) of the Oxazaphosphorine dose then oral 40% w/w of the dosage of the Oxazaphosphorines administered at (2 and 6 hours). - Alternatively: Oral 40% w/w 2 hours prior to therapy then 40% w/w of the dosage of the Oxazaphosphorines at (2 and 6 hours).

	• Oral use should not be used with continuous infusions of Oxazaphosphorines. **Pediatric dosing:** Mesna: 40% (w/w) of Ifosfamide or Cyclophosphamide dose given at (0, 3, 6 and 9 hours). (Total dose = 160% (w/w) of the Oxazaphosphorine dose).
Dosage Adjustment	• **Dosing: Altered Kidney Function: Adult and pediatric** There are no dosage adjustments available. No studies. • **Dosing: Altered hepatic function: Pediatric and adult** There are no dosage adjustments available. No studies.
Contra-indications	• Known hypersensitivity to Mesna or any component of the formulation.
Adverse Drug Reactions	**Mesna alone (frequency not defined):** **Cardiovascular**: Flushing. **Central nervous system**: Dizziness, drowsiness, headache, hyperesthesia, rigors. **Dermatologic:** Skin rash. **Gastrointestinal:** Anorexia, constipation, diarrhea, dysgeusia (with oral administration), flatulence, nausea, unpleasant taste (with oral administration), vomiting. **Local:** Injection site reaction. **Neuromuscular & skeletal:** Arthralgia, back pain. **Ophthalmic:** Conjunctivitis. **Respiratory:** Cough, flu-like symptoms, pharyngitis, rhinitis. **Miscellaneous:** Fever.
Monitoring Parameters	• Monitor urine for the presence of hematuria and proteinuria. • Monitor for signs of hypersensitivity.
Drug Interactions	There are no known significant interactions.
Pregnancy and Lactation	• **Pregnancy:** If Oxazaphosphorine therapy taken during pregnancy then Mesna should be administered to reduce hemorrhagic cystitis. No evidence of embryotoxic or teratogenic effects of Mesna in animals. • **Lactation**: Women should not breastfeed during therapy.
Administration	**Preparation of administration:** • Dilute the volume of Mesna injection in 5% dextrose injection, 0.9% sodium chloride injection, or lactated Ringer's Injection to obtain a final concentration of 20 mg/ml. **IV administration** • Administer as an IV bolus, may also be administered by short infusion or continuous infusion (maintain continuous infusion for 12 to 24 hours after completion of Ifosfamide infusion). • Maintain adequate hydration and urinary output during Ifosfamide (or Cyclophosphamide) treatment. • Mesna can be mixed in the same infusion bag as the Ifosfamide. **Oral administration:**

	• Oral use of Mesna ampoules: Availability of Mesna in urine after oral administration is approximately 50% with 2 hours delayed onset than intravenous route. • The contents of the ampoule should be added to a flavored soft drink (e.g. orange juice). This mixture is stable when refrigerated in a sealed container for 24 hours. **N.B.** Refer to manufacturer PIL for specific considerations.
Storage and Light Sensitivity	Store between (20°C to 25°C). Protect from light. Diluted solution should be stored at 25°C for 24 hours. **N.B.** Refer to manufacturer PIL for specific considerations.
Warnings/ Precautions	• **Hematuria** Monitor urine for hematuria. Severe hematuria despite utilization of Mesna may require Ifosfamide (or cyclophosphamide) dose reduction or discontinuation. Mesna does not prevent hemorrhagic cystitis in all patients. Patients should be monitored accordingly. Sufficient urinary output should be maintained. • **Hypersensitivity Reactions** Hypersensitivity reactions (including anaphylaxis) have been reported. Reactions may occur with the first Mesna exposure, or after several months of treatment. • **Dermatologic Toxicity** The skin and mucosal reactions may be characterized by rash, pruritus, urticaria, erythema, burning sensation, angioedema, periorbital edema, flushing, and stomatitis. Reactions may occur with the first Mesna exposure, or after several months of treatment. • **Benzyl Alcohol Toxicity** Serious adverse reactions including fatal reactions and the “gasping syndrome” occurred in premature neonates and low-birth weight infants who received benzyl alcohol. Symptoms include gradual neurological deterioration, seizures, intracranial hemorrhage, hematological abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse.
Patient Counselling Keys	• If you are allergic to this drug; any part of this drug; or any other drugs, foods, or substances. Tell your doctor about the allergy and what signs you had. • Drink 2 to 4 liters of fluid daily unless your doctor has told you something else. • Have your urine checked as you have been told by your doctor. • If you are breast-feeding. Do not breast-feed while you take this drug and for 1 week after your last dose. • If you have high blood sugar (diabetes), some urine ketone tests may be wrong. Talk with your doctor.

3. Zoledronic acid

Generic Name	Zoledronic acid
Dosage Form/Strengths	• Solution for I.V Infusion: 4mg/100 ml, 5mg/100 ml. • Concentrate for Solution for I.V Infusion: 4 mg/5 ml (0.8mg/ml). • Lyophilized powder for solution for I.V Infusion: 4mg
Route of Administration	IV
Pharmacologic Category	Bisphosphonate Derivative. ATC code: M05BA08
Indications	**N.B.** Refer to literature and specific protocols for all indications. **4mg vials** • Treatment of tumor-induced hypercalcemia (TIH) in adults. • Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumor-induced hypercalcemia) in adult patients with advanced or metastatic malignancies involving bone. • Multiple Myeloma. **5mg vials** • Treatment and prevention of postmenopausal osteoporosis. • Treatment to increase bone mass in men with osteoporosis. • Treatment and prevention of glucocorticoid-induced osteoporosis. • Treatment of Paget's disease of bone in men and women.
Dosage Regimen	**N.B.** Different doses and regimens have been used; consult the literature for specific protocols. **4mg vials** Co-administer oral Calcium supplements of 500 mg and 400 IU vitamin D daily. • **Treatment of tumor-induced hypercalcemia** **IV infusion**: Single dose: 4 mg (over >15 minutes); may be repeated after a minimum of 7 days. • **Bone Metastases; Multiple Myeloma:** **IV infusion**: 4 mg (over >15 minutes) every 3-4 weeks. Infusion given intravenously over no less than 15 minutes: **5mg vials** Patients should receive 1500 mg elemental calcium and 800 IU vitamin D daily. **Treatment of postmenopausal osteoporosis** **IV**: 5mg once yearly (over >15 minutes). **Prevention of Osteoporosis in Postmenopausal Women** **IV**: 5mg once every 2 years (over >15 minutes). **Osteoporosis in Men** **IV**: 5mg once yearly (over >15 minutes). **Treatment and Prevention of Glucocorticoid-Induced Osteoporosis** **IV**: 5mg once yearly (over >15 minutes).

Treatment of Paget's Disease of Bone
IV: 5mg, single dose (over >15 minutes).
Re-treatment may be considered in patients who have relapsed.

Pediatrics: The safety and efficacy in children aged 1 year to 17 years have not been established.

Dosage Adjustment

N.B. Refer to protocol used for specific dose modifications.

Altered kidney function:

- **Multiple myeloma and bone metastases of solid tumors.**

Baseline creatinine clearance (mL/min)	Dose
>60	4 mg
50-60	3.5 mg
40-49	3.3 mg
30-39	3 mg
<30	Not recommended

- **For hypercalcemia of malignancy:**
  - Mild to moderate impairment: No dose adjustment.
  - Severe impairment (serum creatinine > 400 µmol/L or >4.5 mg/dl): Not recommended, no data.

Withhold treatment if renal function deteriorated as follows:

- For patients with normal baseline serum creatinine: an increase of 0.5 mg/dl or 44µmol/l.
- For patients with abnormal baseline creatinine: an increase of 1.0 mg/dl or 88µmol/l.

- **Hepatic impairment:** Limited clinical data in severe hepatic insufficiency. Zoledronic acid is not metabolized hepatically.

Contra-indications

- Hypersensitivity to the active substance, to other Bisphosphonates or to any of the excipients.
- Pregnancy and Breast-feeding.

Adverse Drug Reactions

Significant adverse reactions

- **Renal toxicity:**

Resulting in renal failure, dialysis, and/or death.

- **Mineral and electrolyte abnormalities**

Hypocalcemia is reported and has been life-threatening in some cases. Neurologic adverse events (e.g. tonic clonic seizures, tetany, and numbness) as well as QTc prolongation and cardiac arrhythmias secondary to severe

hypocalcemia may occur. Symptoms of muscle spasms, numbness, and/or tingling, especially around the mouth should be promptly reported.

- **Osteonecrosis of the jaw (ONJ)**

A rare, but serious event that has been associated with IV bisphosphonate therapy.

- **Flu-like symptoms:**

Pyrexia is the most common symptom, but myalgia, arthralgia, arthritis, swollen joints, and/or headache.

- **Atypical bone fractures**

>10%

Cardiovascular: Hypotension (11%), lower extremity edema (5% to 21%).
Dermatologic: Alopecia (12%), dermatitis (11%).
Endocrine & metabolic: Dehydration (5% to 14%), hypokalemia (12%), hypomagnesemia (11%), hypophosphatemia (13%), weight loss (16%)
Gastrointestinal: Abdominal pain (14% to 16%), anorexia (9% to 22%), constipation (27% to 31%), decreased appetite (13%), diarrhea (17% to 24%), nausea (29% to 46%), vomiting (14% to 32%).
Genitourinary: Urinary tract infection (12% to 14%).
Hematologic & oncologic: Anemia (22% to 33%), neutropenia (12%), progression of cancer (16% to 20%).
Infection: Candidiasis (12%).
Nervous system: Agitation (13%), anxiety (11% to 14%), confusion (7% to 13%), depression (14%), dizziness (18%), fatigue (39%), headache (5% to 19%), hypoesthesia (12%), insomnia (15% to 16%), paresthesia (15%), rigors (11%).
Neuromuscular & skeletal: Arthralgia (5% to 21%), asthenia (5% to 24%), back pain (15%), limb pain (14%), myalgia (23%), ostealgia (55%), skeletal pain (12%).
Renal: Renal insufficiency (8% to 15%; up to 40% in patients with abnormal baseline creatinine).
Respiratory: Cough (12% to 22%), dyspnea (22% to 27%).
Miscellaneous: Fever (32% to 44%; most common symptom of acute phase reaction).

1% to 10%

Cardiovascular: Chest pain (5% to 10%).
Endocrine & metabolic: Hypermagnesemia (grade 3: 2%), hypocalcemia (5% to 10%).
Gastrointestinal: Dyspepsia (10%), dysphagia (5% to 10%), sore throat (8%), stomatitis (8%).
Hematologic & oncologic: Granulocytopenia (5% to 10%), pancytopenia (5% to 10%), thrombocytopenia (5% to 10%).
Infection: Infection (nonspecific: 5% to 10%).
Nervous system: Drowsiness (5% to 10%).

	Renal: Increased serum creatinine (grades 3/4: ≤2%). **Respiratory**: Upper respiratory tract infection (10%).
Monitoring Parameters	• Renal function test (serum creatinine) before each dose. • Monitor electrolyte and minerals during treatment such as serum levels of calcium, phosphate and magnesium (short-term supplemental therapy may be needed).
Drug Interactions	• **Aminoglycosides, Loop Diuretics**: Increased risk of hypocalcemia. Monitor serum Calcium closely. • **Nephrotoxic Drugs:** Caution is indicated when Zoledronic acid is used with other potentially nephrotoxic drugs.
Pregnancy and Lactation	**Pregnancy:** Not recommended. There may be a risk of fetal harm (e.g., skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. No adequate and well controlled studies. **Lactation**: Not recommended due to the potential secretion into breast milk.
Administration	**Preparation of administration:** Dilute in 100 mL of sterile 0.9% Sodium Chloride, or 5% Dextrose Injection. **IV administration:** • If refrigerated, allow solution to reach room temperature before administration. • Infuse over at least 15 minutes. Infuse in a line separate from other medications. Flush IV line with 10 mL NS flush following infusion. • Patients must be appropriately hydrated prior to and following treatment. • Acetaminophen after administration may reduce the incidence of acute reaction (eg, arthralgia, fever, flu-like symptoms, myalgia).
Warnings/ Precautions	• Do not co administer with other medicines of the same class, bisphosphonates. • **Hydration and Electrolyte Monitoring** - Patients must be adequately hydrated prior to administration of Zoledronic Acid Injection. Avoid overhydration in patients at risk of cardiac failure. - Loop diuretics should not be used until the patient is adequately rehydrated and should be used with caution in combination with Zoledronic Acid Injection in order to avoid hypocalcemia. - Serum levels of calcium, phosphate, and magnesium, as well as serum creatinine, should be carefully monitored following initiation of therapy with Zoledronic Acid Injection. If hypocalcemia, hypophosphatemia, or hypomagnesemia occur, short-term supplemental therapy may be necessary. • **Renal Impairment** - Zoledronic Acid Injection is excreted intact primarily via the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function.

- Risk factors include: dehydration, pre-existing renal impairment, multiple cycles of Zoledronic Acid and other bisphosphonates as well as use of other nephrotoxic drugs.

- **Osteonecrosis of the Jaw**
  - Osteonecrosis of the jaw (ONJ) has been reported uncommonly in cancer patients treated with Zoledronic Acid Injection. Risk factors include: receiving chemotherapy and corticosteroids. The risk of ONJ may increase with duration of exposure to bisphosphonates.
  - Delay the start of treatment or a new course in patients with unhealed open soft tissue lesions in the mouth, except in medical emergency situations. While on treatment, patients should avoid invasive dental procedures if possible.
  - Patients should maintain good oral hygiene, undergo routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling, non-healing of sores or discharge during treatment with Zoledronic acid.
  - If ONJ developed, consider temporary interruption of Zoledronic acid until the condition resolves.
- **Atypical fractures of the femur**
  - Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. Poor healing of these fractures has also been reported.
  - Patient should report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.
  - Consider discontinuation of Zoledronic Acid therapy in patients suspected to have an atypical femur fracture until evaluation of the patient, based on an individual benefit risk assessment.
- **Hypocalcemia**
  - Cardiac arrhythmias and neurologic adverse events (seizures, tetany, and numbness) have been reported secondary to cases of severe hypocalcemia
  - Serum calcium should be measured and hypocalcemia must be corrected before initiating Zoledronic Acid Injection. Adequately supplement patients with calcium and vitamin D.
- **Hypersensitivity reactions**:
  Rare cases of urticaria and angioedema and very rare cases of anaphylactic reactions/shock have been reported.
- **Effects on ability to drive and use machines:**
  Dizziness and somnolence, may have influence on the ability to drive or use machines. Caution.
- **Influenza-like illness/acute phase reaction**:

	A transient acute phase reaction (e.g. fever, myalgia, headache, extremity pain, nausea, vomiting, diarrhea and arthralgia) may occur, typically within 3 days following the initial infusion; resolution is usually observed in 3 days after symptom onset but can take up to 14 days. • **Musculoskeletal pain** The onset of pain ranged from a single day to several months. Symptoms usually resolve upon discontinuation.
Storage and Light Sensitivity	Store between to 15°C - 30°C. **N.B.** Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• The most common side effects including: anemia, nausea, vomiting, constipation, diarrhea, fatigue, fever, weakness, lower limb edema, anorexia, decreased weight, bone pain, myalgia, arthralgia, back pain, malignant neoplasm aggravated, headache, dizziness, insomnia, paresthesia, dyspnea, cough, and abdominal pain. • Get blood tests as directed by physician during the course of therapy. • Care about good dental hygiene. Tell doctor if symptoms appeared like dental mobility, pain or swelling, non-healing of sores. Tell your doctor if you Plan to have dental surgery or teeth removed. • Administer an oral calcium supplement and a vitamin D daily as directed. • Report any thigh, hip, or groin pain. It is unknown whether the risk of atypical femur fracture continues after stopping therapy. • There have been reports of bronchoconstriction in aspirin-sensitive patients receiving bisphosphonates, including zoledronic acid. Before being given zoledronic acid, patients should tell their doctor if they are aspirin-sensitive. • Zoledronic acid may affect fertility and may harm the baby if used during pregnancy. It is best to use birth control while being treated with zoledronic acid. Do not breastfeed during treatment.

Therapeutic enzymes

1. Asparaginase

Generic Name	Asparaginase
Dosage Form/ Strengths	10,000 IU as lyophilized powder in single-use vials
Route of Administration	IM, IV
Pharmacologic Category	Antitumor antibiotic, Antineoplastic Agent, Enzyme. ATC code: L01XX02
Indications	**N.B.** *Refer to literature and specific protocols for all indications.* • Treatment of acute lymphoblastic leukemia (ALL) in combination therapy. • Non-Hodgkin's lymphoma.
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols.* ***Adults and children older than 1 year*** **IV**: 5,000 IU/m^2 given every third day. ***Children 0 – 12 months old*** Age 6 – 12 months: 7,500 IU/m^2 Age less than 6 months: 6,700 IU/m^2 **Or** ***Adults and children*** **IM, IV**: 6,000 IU/m^2 three times a week for a total of 9 doses.
Dosage Adjustment	**N.B.** *Refer to protocol used for specific dose modifications.* **Dosing: Altered Kidney Function** No dose adjustment is necessary in patients with renal impairment. **Dosing: Altered Hepatic Function** **Mild to moderate hepatic impairment**: No dose adjustment is necessary. **Severe impairment**: Not recommended. **Dose adjustments for toxicities during treatment**

Liver enzymes	Therapy
ALT/AST >3 to 5 times ULN	Continue therapy.
ALT/AST >5 to 20 times ULN	Delay next dose until transaminases <3 times ULN.
ALT/AST >20 times ULN	Discontinue therapy if takes longer than 1 week for transaminases to return to <3 times ULN.

	<table><tr><th>Bilirubin</th><th>Therapy</th></tr><tr><td>Direct bilirubin <3 mg/dL</td><td>Continue therapy.</td></tr><tr><td>Direct bilirubin 3.1 to 5 mg/dL</td><td>Hold Asparaginase and resume when direct bilirubin <2 mg/dL.</td></tr><tr><td>Direct bilirubin >5 mg/dL</td><td>Discontinue Asparaginase</td></tr></table> **Dosing: Adjustment for Toxicity: Adult and pediatric:** • **Pancreatitis:** Severe or hemorrhagic pancreatitis (abdominal pain >72 hours and amylase ≥2 x ULN): Discontinue treatment; further use is contraindicated. • **Thrombosis**: Discontinue in patients with serious thrombotic events. Coagulopathy: Monitor coagulation parameters at baseline and periodically during and after treatment. In patients with severe or symptomatic coagulopathy, initiate treatment with fresh-frozen plasma to replace coagulation factors.
Contra-indications	• Serious allergic reactions to L-asparaginases. • Pancreatitis. • Severe hepatic impairment (bilirubin > 3 times upper limit of normal [ULN]; transaminases > 10 times ULN). • Pre-existing known coagulopathy (e.g. hemophilia). • History of pancreatitis, serious hemorrhage, or serious thrombosis prior to Asparaginase therapy.
Adverse Drug Reactions	**>10%** **Endocrine & metabolic:** Hyperglycemia. **Gastrointestinal**: Nausea, vomiting. **Hepatic**: Increased serum transaminases. **Hypersensitivity**: Hypersensitivity reaction. **Immunologic**: Antibody development. **1% to 10%** **Cardiovascular**: Thrombosis. **Endocrine and metabolic**: Decreased glucose tolerance. **Gastrointestinal**: Abdominal distress, abdominal pain, diarrhea, pancreatitis, stomatitis. **Hematologic and oncologic**: Hemorrhage. **Hepatic**: Hyperbilirubinemia. **Hypersensitivity**: Local hypersensitivity reaction. **Miscellaneous**: Fever.
Monitoring Parameters	**Before therapy:** • Bilirubin and hepatic transaminases.

	• Coagulation parameters (e.g. partial thromboplastin time [PTT], prothrombin time [PT], antithrombin III, and fibrinogen). **After starting therapy:** • Bilirubin and hepatic transaminases. • Blood/urinary glucose. • Coagulation parameters (e.g. PTT, PT, antithrombin III, fibrinogen, and D-dimer). • Lipid profile (amylase, lipase, triglycerides and cholesterol).
Drug Interactions	***Risk D: Consider therapy modification*** Hormonal Contraceptives. **Notes:** • **Methotrexate**: Asparaginase should be administered 24 hours after Methotrexate treatment. This regimen has been shown to reduce the gastrointestinal and hematological effects of Methotrexate and enhance antitumor effects of Methotrexate. • **Cytarabine**: Efficacy of high-dose Cytarabine is reduced by prior administration of asparaginase. However, when Asparaginase was given after Cytarabine a synergistic effect was observed. This effect was most prominent with a treatment interval of about 120 hours. • **Vincristine**: Vincristine should be given before Asparaginase with 3 to 24 hours to minimize toxicity. • **Glucocorticoids**: Concomitant use of glucocorticoids and Asparaginase may increase the formation of blood clots (thrombosis).
Pregnancy and Lactation	**Pregnancy:** There are no adequate and well-controlled studies in pregnant women. It should be given to a pregnant woman only if clearly needed. Effective contraceptive measures should be used while being treated with Asparaginase and for 7 months following completion of treatment. Oral contraceptives are not considered sufficiently safe due to interaction with Asparaginase. **Breastfeeding**: Not recommended due to the potential secretion into breast milk.
Administration	**Preparation of administration** **For IM administration**: Reconstitute in 2 mL. Limit the volume at a single injection site to 2 mL; if greater than 2 mL, use multiple injection sites. **For IV administration:** Reconstitute in 5 mL. DO NOT administer as a bolus dose. **Rate of IV infusion:** Infuse over 30 min-2 hours through side arm of an infusion of Sodium Chloride (0.9%) or Dextrose 5%. **N.B.** Refer to manufacturer PIL for specific considerations.
Emetogenicity	Minimal (<10% frequency of emesis).

Warnings/ Precautions	

Anaphylaxis and Serious Allergic Reactions

Serious allergic reactions may occur. Observe patients for one hour after administration in a setting with agents necessary to treat anaphylaxis (for example, epinephrine, oxygen, intravenous steroids, and antihistamines). Discontinue if serious allergic reactions occurred.

Pancreatitis

Pancreatitis, in some cases fulminant or fatal, may occur. Evaluate patients with abdominal pain, nausea, vomiting and anorexia for evidence of pancreatitis. Patients with severe hypertriglyceridemia are at increased risk of developing acute pancreatitis. Discontinue permanently if pancreatitis occurred.

Hyperglycemia

Asparaginase may induce hyperglycemia due to decreased insulin production and impaired insulin receptor function. The syndrome is generally self-limiting. Glucose intolerance may be sometimes irreversible. Cases of diabetic ketoacidosis have been reported. Monitor serum glucose.

Coagulopathy and Thrombosis

Increased prothrombin time increased partial thromboplastin time, and hypofibrinogenemia may occur due to inhibition of protein synthesis. CNS hemorrhages have been observed. Monitor coagulation parameters at baseline and periodically during and after treatment. If severe or symptomatic coagulopathy, initiate treatment with fresh-frozen plasma to replace coagulation factors. Serious thrombotic events may occur. Discontinue if serious thrombotic events occurred.

Hepatotoxicity and Abnormal Liver Function

In rare cases severe liver impairment has been developed, including cholestasis, icterus, hepatic necrosis and hepatic failure with fatal outcome. Hepatotoxicity and abnormal liver function may occur. Liver parameters should be monitored closely before and during treatment with Asparaginase. Fatty changes in the liver have been documented on biopsy.

Neurotoxicity

Posterior reversible encephalopathy syndrome (PRES) has been developed after treatment with Asparaginase in combinations. PRES is a neurological disorder with clinical symptoms of headache, seizures, visual disturbances, altered mental status, and hypertension. Symptoms can be nonspecific, and diagnosis requires confirmation by radiological procedures. Interrupt use if PRES is suspected or diagnosed. Control blood pressure promptly and monitor closely for seizure activity.

Impaired protein synthesis

	Asparaginase induces protein synthesis inhibition. Therefore, hypoalbuminemia and edema can occur. Decreased serum thyroxin-binding globulin and transitory secondary hypothyroidism have been reported. Hyperglycemia may develop due to decreased insulin production. **Dyslipidemia** Mild to moderate changes in blood lipid values are very commonly observed in patients treated with asparaginase. Concomitant administration of glucocorticoids may be a contributing factor. in rare cases severe hypertriglyceridemia (triglycerides > 1,000 mg/dl) has been reported which increases the risk of development of acute pancreatitis. **Hyperammonemia** Plasma ammonia levels should be determined in all patients with unexplained neurologic symptoms or severe and prolonged vomiting. In case of hyperammonemia with severe clinical symptoms, therapeutic and pharmacological measures that rapidly reduce plasma ammonia levels (e.g. protein restriction and hemodialysis), reverse catabolic states and increase removal of nitrogen wastes should be initiated and expert advice sought.
Storage and Light Sensitivity	• Keep vials refrigerated at 2-8°C. • Use reconstituted solution within eight hours if kept at 2-8°C or discard sooner if it becomes cloudy. **N.B.** Refer to manufacturer PIL for specific considerations.
Patient Counseling Keys	• Tell your doctor before starting therapy if you had previously inflammation of the pancreas (pancreatitis), severe liver function problems, a blood clotting disorder (such as hemophilia), high blood sugar. • Tell your doctor if you had a severe reaction after previous asparaginase treatment. • Do not drive or use machines when taking this medicine because it may make you feel drowsy, tired, or confused. • Asparaginase may induce hyperglycemia because of decreased insulin production. Monitor blood glucose regularly. • Signs of a pancreas problem (pancreatitis) like very bad stomach pain, very bad back pain, or very bad upset stomach or throwing up. • Call your doctor right away if you have signs of a blood clot like chest pain or pressure; coughing up blood; shortness of breath; swelling, warmth, numbness, change of color, or pain in a leg or arm; or trouble speaking or swallowing.
Sequence of Administration	• This drug is cell cycle specific, with the greatest activity in the G1 phase. • Non-vesicant. When combined with the following medicines:

- **Methotrexate**: Asparaginase should be administered 24 hours after Methotrexate treatment.
- **Cytarabine**: Asparaginase should be given after Cytarabine with a treatment interval of about 120 hours.
- **Vincristine**: Vincristine should be given before Asparaginase within 3 to 24 hours to minimize toxicity.

Topoisomerase Inhibitors

1. Etoposide

Generic Name	Etoposide
Dosage Forms/ Strengths	Concentrate for Solution for I.V Infusion 20mg/1ml, 100mg/5ml Capsule: 50mg
Route of Administration	Oral, IV
Pharmacologic Category	Antineoplastic Agent, Podophyllotoxin Derivative; Topoisomerase II Inhibitor ATC: L01CB01
Indications	**N.B.** *Refer to literature and specific protocols for all indications.* Used in combination with other chemotherapeutic agents for the treatment of: • Small cell lung cancer (Oral and IV): Treatment (first line) of small cell lung cancer. • Testicular cancer (IV): Treatment of refractory testicular tumors (injection only). • Hodgkin's lymphoma. • Non-Hodgkin's lymphoma. • Acute myeloid leukaemia. • Gestational trophoblastic neoplasia. • Ovarian cancer.
Dosage Regimen	**N.B.** *Different doses and regimens have been used; refer to literature for specific protocols.* **Adult Dosing** **For the treatment of refractory testicular cancer, in combination with other chemotherapeutic agents** IV: 50-100 mg/m^2 once daily on days 1 to 5 in combination with other chemotherapeutic agents, every 3 to 4 weeks. **For the first-line treatment of SCLC, in combination with other chemotherapeutic agents** IV: 35 mg/m^2 once daily on days 1 to 4 in combination with other chemotherapeutic agents, every 3 to 4 weeks. ***IV to oral conversion:*** Due to poor bioavailability, oral doses should be twice the IV dose (and rounded to the nearest 50 mg). **Pediatric dosing** Hodgkin's lymphoma; non-Hodgkin's lymphoma; acute myeloid leukaemia: 75 to 150 mg/m^2 /day for 2 to 5 days in combination with other antineoplastic agents.
Dosage Adjustment	**N.B.** *Refer to the protocol used for specific dose modifications.* **Dosing: Altered Kidney Function:** Oral, IV: CrCl >50 mL/minute: No adjustment required. CrCl 15 to 50 mL/minute: Administer 75% of dose. CrCl <15 mL minute: Data not available; consider further dose reductions. **Dosing: Hepatic Impairment:**

	Bilirubin 1.5 to 3 mg/dL or AST greater than 3 times the upper limit of normal: Reduce the etoposide dose by 50%. Bilirubin 3 to 5 mg/dL: Reduce the etoposide dose by 75%. Bilirubin greater than 5 mg/dL: Hold etoposide. **Dosing: Adjustment for Toxicity:** **Oral, IV:** • ANC <500/mm^3 or platelets <50,000/mm^3: Withhold treatment until recovery. • Hypotension: Interrupt infusion and administer IV hydration and supportive care; decrease infusion rate upon reinitiation. • Infusion (hypersensitivity) reactions: Interrupt infusion (medications for the treatment of anaphylaxis should be available for immediate use during etoposide IV administration). • Severe adverse reactions (nonhematologic): Reduce dose or discontinue treatment.
Contra-indications	• Hypersensitivity to etoposide or any component of the formulation • Severe leukopenia or thrombocytopenia • Severe hepatic impairment; severe renal impairment
Adverse Drug Reactions	**Bone marrow suppression:** Severe myelosuppression, with resulting infection or bleeding, may occur. **>10%** **Dermatologic**: Alopecia (8% to 66%) **Gastrointestinal**: Nausea and vomiting (31% to 43%), anorexia (10% to 13%), diarrhea (1% to 13%) **Hematologic & oncologic**: Leukopenia (60% to 91%; grade 4: 3% to 17%; nadir: 7 to 14 days; recovery: by day 20), thrombocytopenia (22% to 41%; grades 3/4: 1% to 20%; nadir: 9 to 16 days; recovery: by day 20), anemia (≤33%) **1% to 10%** **Cardiovascular**: Hypotension (1% to 2%; due to rapid infusion) **Central nervous system**: Peripheral neuropathy (1% to 2%) **Gastrointestinal**: Stomatitis (1% to 6%), abdominal pain (≤2%) **Hepatic**: Hepatotoxicity (≤3%) **Hypersensitivity**: Anaphylactoid reaction (intravenous: 1% to 2%; oral capsules: <1%; including bronchospasm, chills, dyspnea, fever, tachycardia)
Monitoring Parameters	• CBC with differential • Liver function test • Kidney function test • Monitor for signs of an infusion reaction. • Monitor adherence.
Drug Interactions	***Risk X: Avoid combination*** Abrocitinib, Baricitinib, BCG Products, Brivudine, Chikungunya Vaccine (Live), Chloramphenicol (Systemic), Cladribine, Deucravacitinib, Dipyrone, Etrasimod,

	Fexinidazole, Filgotinib, Natalizumab, Nadofaragene Firadenovec, Pimecrolimus, Poliovirus Vaccine (Live/Trivalent/Oral), Mumps- Rubella- or Varicella-Containing Live Vaccines, Ruxolitinib (Topical) Tacrolimus (Topical), Tertomotide, Typhoid Vaccine, Upadacitinib, Vaccines (Live), Yellow Fever Vaccine. ***Risk D: Consider therapy modification*** Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), Cyclosporine (Systemic), CYP3A4 Inducers (Strong), Deferiprone, Denosumab, Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b Sipuleucel-T Vaccines (Inactivated/Non-Replicating), Barbiturates (phenobarbital), Carbamazepine, Phenytoin Rifampicin.
Pregnancy and Lactation	**Pregnancy**: Avoid pregnancy while taking etoposide as it causes fetal harm in pregnant women. **Lactation**: Due to the risk of serious adverse reactions in nursing infants, women should discontinue breast-feeding during etoposide therapy.
Administration	**Hazardous** agent (NIOSH 2016 [group 1]): IARC Group 1 carcinogen (Carcinogenic to humans). Use appropriate precautions for receiving handling, storage, preparation, dispensing, transporting, administration, and disposal. **Administration: IV** • IV: For slow IV infusion only; do not administer by rapid IV injection or other routes due to possible severe toxicity. Administer standard doses over at least 60 minutes to minimize the risk of hypotension and toxicity. Solutions may be administered at infusion not to exceed 100 mg/m^2/hour (or 3.3 mg/kg/hour) • Etoposide is an irritant; tissue irritation and inflammation have occurred following extravasation; avoid extravasation. **Preparation for Administration** • **IV:** Etoposide should be diluted to a concentration of 0.2 to 0.4 mg/mL in D5W or NS for administration. Diluted solutions have concentration-dependent stability. Concentrations >0.4 mg/mL are very unstable and may precipitate within a few minutes. **Administration: Oral** • Doses ≤200 mg/day may be administered as a single once daily dose; doses >200 mg should be given in 2 divided doses. Taken with or without food. • If necessary, the injection may be used to prepare an oral solution for oral administration or by mixing dose with orange juice, apple juice, or lemonade (**NOT** grapefruit juice) at a final concentration not to exceed 0.4 mg/mL. **N.B.** Refer to manufacturer PIL foe specific considerations.
Emetogenicity	Parentral: Low emetic risk (10%–30% frequency of emesis). Oral: Moderate to high emetic risk (≥30% frequency of emesis).
Warnings/ Precautions	• **Bone marrow suppression**: Severe myelosuppression with resulting infection or bleeding may occur. Myelosuppression is dose related and dose limiting. Granulocyte and platelet nadirs typically occur 7 to 14 days or 9 to 16 days, respectively, after administration; hematologic recovery usually occurs by day

	20. • **Extravasation**: Etoposide IV is an irritant; tissue irritation and inflammation have occurred following extravasation. • **Hypersensitivity**: May cause anaphylactic-like reactions manifested by chills, fever, tachycardia, bronchospasm, dyspnea, and hypotension. In addition, facial/tongue swelling, coughing, chest tightness, cyanosis, laryngospasm, diaphoresis, hypertension, back pain, loss of consciousness, and flushing have also been reported less commonly. Incidence is primarily associated with IV administration (up to 2%) compared to oral administration (<1%). • **Hypotension**: Hypotension may occur due to rapid administration. • **Secondary malignancies**: Secondary acute leukemias have been reported with etoposide, either as monotherapy or in combination with other chemotherapy agents. • Hypoalbuminemia: Use with caution in patients with low serum albumin; may increase risk for toxicities. • **Older adult:** Patients ≥65 years of age may be more likely to develop severe myelosuppression and/or GI effects. • **Pediatrics**: The use of concentrations higher than recommended was associated with higher rates of anaphylactic-like reactions in children. • **Alcohol**: Injectable formulation contains alcohol (~30% to 33% v/v); may contribute to adverse reactions, especially with higher etoposide doses. • **Benzyl alcohol and derivatives**: Some dosage forms may contain benzyl alcohol; large amounts of benzyl alcohol (≥99 mg/kg/day) have been associated with a potentially fatal toxicity ("gasping syndrome") in neonates. See product labeling. • **Polysorbate 80**: Some dosage forms may contain polysorbate 80 (also known as Tweens). Hypersensitivity reactions, usually a delayed reaction, have been reported following exposure.
Storage and Light Sensitivity	• Store oral capsules at 2°C to 8°C or at room temperature according to product. • Injection: Store intact vials at 20°C to 25°C; do not freeze. Stability for solutions diluted for infusion in D5W or NS (in glass or plastic containers) varies based on concentration; 0.2 mg/mL solutions are stable for 96 hours at room temperature and 0.4 mg/mL solutions are stable for 24 hours at room temperature (precipitation may occur at concentrations above 0.4 mg/mL). • Retain vial and oral form in original package to protect from light. **N.B.** Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• This drug induces low blood cell counts. Avoid infections and bleeding causes. • This drug is Carcinogenic. Teratogenic. • Refer to the doctor in case of signs of infection, bleeding, allergic reaction, high or low blood pressure or shortness of breath.
Sequence of Administration	• Cell cycle specific. • Irritant. • When combined with vincristine, Etoposide may be administered first.

2. Irinotecan

Generic Name	Irinotecan
Dosage Form/ Strengths	Concentrate for Solution For I.V Infusion: 40mg/2ml, 100mg/5ml.
Route of Administration	IV
Pharmacologic Category	Antineoplastic Agent; Topoisomerase I Inhibitor ATC code: L01CE02
Indications	**N.B.** *Refer to literature and specific protocols for all indications used.* • Advanced colorectal cancer in adults (as a first line or for recurrent or progressive disease following initial fluorouracil-based treatment).
Dosage Regimen	**N.B.** *Different doses and regimens have been used; consult the literature for specific protocols.* **Adult dosing** **In monotherapy** (for previously treated patient with fluorouracil-based treatment): - 350 mg/m² administered as IV infusion every three weeks. - **Or** 125 mg/m² IV infusion on days 1, 8, 15, 22 then 2-week rest. **In combination therapy** (for previously untreated patient): - 180 mg/m² administered once every 2 weeks as followed by infusion with Folinic acid and 5-Fluorouracil. - **Or** 125 mg/m² IV infusion on days 1, 8,15, 22 then 2-week rest. **Pediatrics**: The safety and efficacy of irinotecan in children have not yet been established. No data are available.
Dosage Adjustment	**N.B.** *Refer to protocol used for specific dose modifications.* **Dosing: Altered Kidney Function: Adult** Specific dose adjustments are not available; Caution. Irinotecan is not recommended for use in patients on dialysis. **Dosing: Hepatic Impairment: Adult** Monotherapy: Bilirubin up to 1.5 times ULN: 350 mg/m². Bilirubin 1.5 to 3 times ULN: 200 mg/m² every 3 weeks Bilirubin ≥ 3 times ULN: Avoid use. Combination therapy: No data are available in patients with hepatic impairment
Contra-indications	- Hypersensitivity to the active substance or to any of the excipients. - Severe bone marrow failure. - Pregnancy. - Bilirubin >3 times the upper limit of the normal range.

	- Chronic inflammatory bowel disease and/or bowel obstruction until resolution of obstruction.
Adverse Drug Reactions	**>10%** **Cardiovascular**: Vasodilation (9% to 11%) **Central nervous system**: Cholinergic syndrome (47%; includes diaphoresis, flushing, increased peristalsis, lacrimation, miosis, rhinitis, sialorrhea), pain (23% to 24%), dizziness (15% to 21%), insomnia (19%), headache (17%), chills (14%) **Dermatologic**: Alopecia (46% to 72%), diaphoresis (16%), skin rash (13% to 14%) **Endocrine & metabolic**: Weight loss (30%), dehydration (15%) **Gastrointestinal**: Diarrhea (late: 83% to 88%, grades 3/4: 14% to 31%; early: 43% to 51%, grades 3/4: 7% to 22%), nausea (70% to 86%), abdominal pain (57% to 68%), vomiting (62% to 67%), abdominal cramps (57%), anorexia (44% to 55%), constipation (30% to 32%), mucositis (30%), flatulence (12%), stomatitis (12%) Hematologic & oncologic: Anemia (60% to 97%; grades 3/4: 5% to 7%), leukopenia (63% to 96%, grades 3/4: 14% to 28%), thrombocytopenia (96%, grades 3/4: 1% to 4%), neutropenia (30% to 96%; grades 3/4: 14% to 31%) **Hepatic**: Increased serum bilirubin (84%), increased serum alkaline phosphatase (13%) **Infection**: Infection (14%) **Neuromuscular & skeletal**: Weakness (69% to 76%), back pain (14%) **Respiratory**: Dyspnea (22%), cough (17% to 20%), rhinitis (16%) **Miscellaneous**: Fever (44% to 45%) **1% to 10%** **Cardiovascular**: Edema (10%), hypotension (6%), thromboembolism (5%) **Central nervous system**: Drowsiness (9%), confusion (3%) **Gastrointestinal**: Abdominal distention (10%), dyspepsia (10%) **Hematologic & oncologic**: Febrile neutropenia (grades 3/4: 2% to 6%), hemorrhage (grades 3/4: 1% to 5%), neutropenic infection (grades 3/4: 1% to 2%) **Hepatic**: Increased serum AST (10%), ascites (grades 3/4: ≤9%), jaundice (grades 3/4: ≤9%) **Respiratory**: Pneumonia (4%)
Monitoring Parameters	• CBC with differential • Liver function test. • Pregnancy test. • Monitor for hypersensitivity reactions, infusion site, bowel movements and hydration status, signs/symptoms of pulmonary toxicity.
Drug Interactions	***Risk X: Avoid combination*** 5-Aminosalicylic Acid Derivatives, Atazanavir, Baricitinib, BCG (Intravesical), BCG Products, Brivudine, Cladribine, Dengue Tetravalent Vaccine (Live),

	Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Fusidic Acid (Systemic), Itraconazole, Ketoconazole (Systemic), Mumps- Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Poliovirus Vaccine (Live/Trivalent/Oral), Ritlecitinib, Ruxolitinib (Topical), Sacituzumab Govitecan, St John's Wort, Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Typhoid Vaccine, UGT1A1 Inhibitors, Upadacitinib, Vaccines (Live), Yellow Fever Vaccine. ***Risk D: Consider therapy modification*** Coccidioides immitis Skin Test, COVID-19 Vaccine (Adenovirus Vector), COVID-19 Vaccine (mRNA), Strong CYP3A4 Inducers (eg. Barbiturates (phenobarbital), Carbamazepine, Phenytoin, Rifampicin), Strong CYP3A4 Inhibitors (eg. Strong CYP3A4 Inducers Clarithromycin, Itraconazole, Ketoconazole, Posaconazole), Deferiprone, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating). **Notes:** CYP3A4 enzyme inducers may decrease exposure to irinotecan the active metabolite; enzyme inhibitors may increase exposure. It's recommended to avoid combination.
Pregnancy and Lactation	**Pregnancy:** Can cause fetal harm when administered to a pregnant woman. Avoid if either partner is receiving Irinotecan due to embryotoxic and teratogenic properties. **Lactation:** Limited data, Avoid because of the potential for adverse reactions in nursing infants.
Administration	**Hazardous agent** (NIOSH 2016 [group 1]): Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. **Administration: IV** Administer by IV infusion, usually over 30-90 minutes. Irritant. **Preparation for Administration: Adult** Dilute in D_5W (preferred) or NS to a final concentration of 0.12 to 2.8 mg/mL. N.B. Refer to manufacturer PIL for specific considerations.
Emetogenicity	Moderate emetic risk: (>30%–90% frequency of emesis).
Warnings/ Precautions	• **Diarrhea and Cholinergic Reactions**: - Acute cholinergic syndrome may appear (as early diarrhea and various other signs and symptoms such as sweating, abdominal cramping, myosis and salivation). Usually transient and may be accompanied by cholinergic symptoms. Consider prophylactic or therapeutic administration of 0.25 mg to 1 mg of IV or subcutaneous atropine (unless clinically contraindicated). - Delayed diarrhea (generally occurring more than 24 hours after administration) can occur. Monitor and replace fluid and electrolytes. The recommended antidiarrheal treatment consists of high doses of loperamide (4

	mg for the first intake and then 2 mg every 2 hours until 12 hours after the last liquid stool. Don't exceed 48 consecutive hours at these doses, because of the risk of paralytic ileus,). Use antibiotic support for ileus and fever. In patients who experienced severe diarrhea, a reduction in dose is recommended for subsequent cycles • **Myelosuppression**: Severe neutropenia may occur. Manage promptly with antibiotic support. Interrupt Irinotecan and reduce subsequent doses if necessary. • **Liver impairment**: Liver function tests should be performed at baseline and before each cycle. Caution in elderly. • **Respiratory disorders:** Fatal cases of interstitial pulmonary disease–like events have been reported with single-agent and combination therapy. Risk factors include preexisting lung disease, use of pulmonary toxic medications, radiation therapy, or colony-stimulating factors. • **Extravasation:** Irinotecan is not a vesicant but irritant. Avoid extravasation, monitor the infusion site for signs of inflammation. If extravasation occur, flushing the site and application of ice is recommended. • **Performance Status 2 baseline patients:** Increased toxicity are observed in these patients including higher rates of hospitalization, neutropenic fever, thromboembolism, first-cycle treatment discontinuation, and early deaths. • **Irradiation therapy:** Increased risk of myelosuppression. Dose adjustments may be necessary. • **Renal Impairment or Failure:** Usually in patients who became volume depleted from severe vomiting and/or diarrhea. • **Conventional vs liposomal formulation dosing:** Irinotecan (conventional) and irinotecan (liposomal) are NOT interchangeable. Dosing differs between formulations; verify intended product and dose prior to preparation and administration. • **Contains sorbitol;** do not use in patients with hereditary fructose intolerance.
Storage and Light Sensitivity	• Store intact vials at 15°C to 30°C. Protect from light; retain vials in original carton until use. • Diluted solution may be stored for up to 72 hours at 2°C to 8°C. Protect from light. **N.B.** Refer to manufacturer PIL for specific considerations.
Patient Counselling Keys	• Call your doctor if gastrointestinal complications. • This drug may cause you more liable to infections and bleeding. Caution. • This drug causes teratogenicity. Avoid getting pregnant during treatment.
Sequence of Administration	• Irritant. • Cell cycle phase-specific (S-phase). • When combined with Cisplatin, Irinotecan should be given second for better response. • When combined with Fluorouracil, Irinotecan should be given first for additive

	efficacy and less toxicity.
Pharmaco-genomics	**UGT1A1** • UGT1A1 is the primary enzyme responsible for the glucuronidation and inactivation of SN-38, which is the active metabolite of irinotecan. • Patients with Both the UGT1A1*6 and *28 variants have increased risk of severe or life-threatening neutropenia.

3. Topotecan

Generic Name	Topotecan
Dosage Form/ Strengths	Lyophilized powder for I.V infusion: 4mg Concentrate for Solution for I.V Infusion: 4mg (1mg/ml)
Route of Administration	IV
Pharmacologic Category	Camptothecin; Antineoplastic Agent, Topoisomerase I Inhibitor. ATC code: L01CE01.
Indications	• **Ovarian cancer, metastatic:** after failure of first-line or subsequent therapy. • **Small cell lung cancer relapsed or progressive:** for whom re-treatment with the first- line regimen after progression is not considered appropriate. • **Carcinoma of the cervix, recurrent after radiotherapy, and for patients with Stage IVB disease:** in combination with Cisplatin. **Other indications:** Ewing Sarcoma, Soft tissue sarcoma.
Dosage Regimen	**Adult dosing** • **Ovarian cancer, metastatic**: IV: 1.5 mg/m^2/day for 5 consecutive days every 21 days, continue until disease progression or unacceptable toxicity. • **Small cell lung cancer, relapsed or progressive:** IV: 1.5 mg/m^2/day for 5 consecutive days every 21 days, continue until disease progression or unacceptable toxicity. • **Cervical cancer:** IV: 0.75 mg/m^2/day for 3 days (days 1, 2, and 3; in combination with Cisplatin 50 mg/m^2 on day 1 only every 21 days for a maximum of 6 cycles (in non-responders) or until disease progression or unacceptable toxicity. **Pediatric dosing** Safety and effectiveness in pediatric patients have not been established.
Dosage Adjustment	**Dosing: Altered Kidney Function: Adult** **IV (single agent Topotecan)** • CrCl ≥40 mL/minute: No dosage adjustment necessary. • CrCl 20 to 39 mL/minute: Reduce dose to 0.75 mg/m^2/dose • CrCl <20 mL/minute: the dose is not recommended. **Dosing: Hepatic Impairment: Adult** • Mild or moderate impairment: No dosage adjustments necessary. • Severe impairment (serum bilirubin ≥10 mg/dl): Not recommended due to insufficient data. **Hematological Toxicity** Do not administer subsequent cycles until neutrophils recover to greater

	than 1,000/mm^3 (or 1500/mm^3 in combination treatment), platelets recover to greater than 100,000/mm^3, and hemoglobin levels recover to greater than or equal to 9 g/dL. **IV as a single agent** ○ Neutrophil counts less than 500/mm^3: Reduce the dose to 1.25 mg/m^2 /day (or subsequently down to 1.0 mg/m^2 /day if necessary), or administer granulocyte-colony stimulating factor (G-CSF) starting no sooner than 24 hours following the last dose. ○ Platelet counts less than 25,000/mm^3 during previous cycle: Reduce the dose to 1.25 mg/m^2/day. **IV in a combination** ○ Febrile neutropenia (neutrophil counts less than 1,000/mm^3 with temperature ≥38.0°C): Reduce the dose to 0.6 mg/m2 /day (and further to 0.45 mg/m^2 if necessary), or administer G-CSF starting no sooner than 24 hours following the last dose. ○ Platelet counts less than 25,000/mm^3 during previous cycle: Reduce the dose to 0.6 mg/m^2 /day (and further to 0.45 mg/m^2 if necessary).
Contra-indications	• Severe hypersensitivity to Topotecan or any component of the formulation. • Severe bone marrow depression prior to starting first course, as evidenced by baseline neutrophils <1.5 x 10^9/l and/or a platelet count of <100 x 10^9/l.
Adverse Drug Reactions	**Bone Marrow Suppression.** **Neutropenic Colitis.** **Interstitial Lung Disease.** **Extravasation.** **>10%** **Central nervous system**: Fatigue **Dermatologic**: Alopecia **Gastrointestinal**: Nausea, diarrhea, vomiting, anorexia. **Hematologic & oncologic**: Anemia, neutropenia, thrombocytopenia, febrile neutropenia, neutropenic infection. **1% to 10%** **Central nervous system**: Pain. **Gastrointestinal**: Abdominal pain, constipation, intestinal obstruction. **Hepatic**: Increased serum alanine aminotransferase. increased serum aspartate aminotransferase, increased serum bilirubin. **Neuromuscular & skeletal**: Asthenia. **Respiratory**: Dyspnea, pneumonia. **Miscellaneous**: Fever, sepsis.
Monitoring Parameters	• CBC with differential platelet count, and hemoglobin with each dose. • Monitor for symptoms of interstitial lung disease (e.g. cough, fever, dyspnea and/or hypoxia), diarrhea symptoms or infusion site reactions. • Renal and liver function test (bilirubin test) may be assessed.

Drug Interactions	***Risk X: Avoid combination*** BCG (Intravesical), BCRP/ABCG2 Inhibitors, Chloramphenicol (Systemic), Cladribine, Dipyrone, Fexinidazole, Lasmiditan, Leniolisib, Pacritinib, P-glycoprotein/ABCB1 Inhibitors, Sparsentan, Taurursodiol, Velpatasvir, Voxilaprevir. ***Risk D: Consder therapy modification*** Deferiprone, Erdafitinib, Fosphenytoin-Phenytoin, Granulocyte Colony-Stimulating Factors, Lenograstim, Lipegfilgrastim, Palifermin, Platinum Derivatives, Ropeginterferon Alfa-2b.
Pregnancy and Lactation	**Pregnancy:** Topotecan can cause fetal harm when administered to a pregnant woman. Use an effective method of contraception for male or female patients. **Lactation**: Avoid due to the potential serious adverse reactions in the breastfed infant.
Administration	**Hazardous agent** (NIOSH 2016 [group 1]): Use appropriate precautions for receiving, handling, storage, preparation, dispensing, transporting, administration, and disposal. **IV administration** • Administer IV over 30 minutes. For combination chemotherapy with Cisplatin, administer pretreatment hydration. **Extravasation** • Topotecan intravenous is an irritant. Leakage of Topotecan outside the vein (extravasation) injuries (some severe) have been reported with intravenous Topotecan; if extravasation occurs, stop infusion immediately and manage appropriately. • Ensure proper needle or catheter placement before and during infusion. Avoid extravasation. **Preparation of administration** • **Powder**: Reconstitute with 4 ml water for injections. The clear, reconstituted solution is yellow to yellow green in color and provides 1 mg of topotecan per ml. Further dilute as follows. • **Concentrate**: Dilute with either sodium chloride (0.9%) solution or glucose (5%) solution for injection, to obtain a final concentration of between 25 and 50mcg/ml.
Warnings/ Precautions	**Bone marrow suppression** • Topotecan can cause severe suppression of blood cell production. Neutropenic fever occurred; sepsis (sometimes fatal) and anemia (grades 3 or 4) have been reported. Frequently monitor blood counts. Only give the

	first cycle to patients with baseline neutrophils ≥1,500/mm^3, platelets ≥100,000/mm^3 and a hemoglobin level of ≥9 g/dl. • Hematologic toxicity may require treatment interruption, dosage reduction, and/or growth factor support. **Hypersensitivity** • Allergic reactions, including allergic reaction, anaphylactic reaction, and angioedema have been reported. **Neutropenic enterocolitis** • Topotecan-induced neutropenia may lead to fatal typhlitis (neutropenic enterocolitis); consider the possibility of typhlitis in patients presenting with neutropenia, fever, and abdominal pain. **Pulmonary toxicity** • Lung inflammation (interstitial lung disease), including fatal cases, has been reported. Monitor for lung signs/symptoms indicating interstitial lung disease; permanently discontinue topotecan in patients with confirmed interstitial lung disease diagnosis. • Risk factors for interstitial lung disease include a history of interstitial lung disease, pulmonary fibrosis, lung cancer, chest radiation, or the use of colony-stimulating factors or medications associated with lung toxicity.
Emetogenicity	Low emetic risk: IV (10% to 30%)
Storage and Light Sensitivity	• Solution for injection: Store intact vials at 2°C to 8°C. • Lyophilized powder: Store intact vials at 20°C to 25°C. • Protect from light. • Store reconstituted product diluted for infusion at approximately 20°C to 25°C protected from light for no more than 24 hours. Discard after 24 hours.
Patient Counseling Keys	• This medicine lower blood cell counts. Avoid causes of infection and bleeding. Frequently monitor blood counts. • Contact doctor immediately if symptoms of lung toxicity (cough, fever, dyspnea and/or hypoxia), gastrointestinal symptoms occurred (Diarrhea, abdominal pain), hypersensitivity reactions. • Don't use this medicine while pregnancy or breastfeeding. Talk with doctor.
Sequence of Administration	• Cell cycle specific: S-phase • Irritant, extravasation may occur.

Alphabetical List of Content

Sources

- The Egyptian Drug Authority database for drugs and pharmaceutical products, available on the official website, https://www.edaegypt.gov.eg/
- The United Kingdom, drug authority, Medicines and Healthcare Products Regulatory Agency (MHRA) https://products.mhra.gov.uk/
- The United States Food and Drug Administration, the federal agency of the Department of Health and Human Services, www.accessdata.fda.gov
- Lexicomp Online, reference handbooks, and desktop software, as a source of drugs full monographs, by Wolters Kluwer Health, www.lexicomp.com
- The searchable version of the complete Anatomical Therapeutic Classification (ATC) index with Defined Daily Dose (DDDs), by the World Health Organization (WHO), www.whocc.no/atc_ddd_index/
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5995553/
- https://www.jhoponline.com/breast-cancer-articles?view=article&artid=13240:top-13240&catid=3321