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

Egyptian National Blood Disorders Formulary

2025

Code: EDA.DUPP. Formulary.005
Version No: 1.0
Issue Date: 2025

Contents

Preface

The Egyptian National 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 Pharmacy Practice Guidelines and National Drug Lists.

This 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 clinical 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
(Blood disorders)

The Egyptian Drug Formulary (Blood disorder medications) contains a list of medicines registered in the Egyptian drug database included in the essential medicines list or widely used in 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.

The Egyptian National Drug Formulary (Blood disorder medications) 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: labeled indications.
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 concentrations, compatibility with diluents, infusion rate, precautions during administration), Oral (food correlation)].
14. Warnings/Precautions.
15. Storage conditions

- 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.

N.B. Referral to the product Leaflet is needed for other specific formulation considerations.

Blood Disorders Medications Formulary

This document includes medications that contribute in management of blood disorders. Therapeutic classes include Antianemia including Iron preparation and other antianemics, Anticoagulants including Direct Thrombin inhibitors, Heparins, Direct Oral Anticoagulants, Vitamin K antagonists and Other anticoagulants, Antihemophilia medications, Antihemorrhagics, Antiplatelets, and Iron Chelators.

Acknowledgment

The General Administration of Drug Utilization and Pharmacy Practice expresses its deepest appreciation to **Dr. Ali Elghamrawy, Chairman of the Egyptian Drug Authority (EDA),** for his remarkable leadership and relentless dedication to advancing pharmaceutical services in Egypt.

We are extremely grateful for **Dr. Shereen Abdelgawad, Head of Pharmaceutical Care Central Administration,** for her contributions to the completion of this work. Dr. Abdelgawad has been instrumental in ensuring all goals and objectives were achieved. Her commitment to enhancing pharmaceutical care services and advocating for the rational use of medications is essential in safeguarding patient safety. We are deeply thankful for her support.

The development of the Egyptian National Drug Formulary is fostered by the exceptional expertise and insightful contributions of the **Members of the Pharmacy Practice Guides and National Drug Lists Committee - EDA.** Their rigorous scientific review, advice, and recommendations have been pivotal in ensuring that this work adhere to the highest standards of quality and effectiveness. We extend our sincere gratitude for their remarkable contributions to this important endeavor.

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

Contributors

Chief Editor	
Dr. Nesma Atef Sarhan Manager of Egyptian Drug Formulary Unit at Drug Utilization and Pharmacy Practice General Administration-EDA	
Workforce Team (Ordered Alphabetically)	
Dr. Abdulrahman Amin Manager of NO HARMe Unit at Drug Utilization and Pharmacy Practice General Administration-EDA	**Dr. Ghada Amged** Member of Drug Utilization and Pharmacy Practice General Administration-EDA
Dr. Lamis Diaa Manager of Medication Consulting Unit at Drug Utilization and Pharmacy Practice General Administration-EDA	**Dr. Noha Anis** Manager of Oncology Pharmacy Unit at Drug Utilization and Pharmacy Practice General Administration-EDA
Dr. Shimaa Sayed Manager of Medication Management Unit- Drug Utilization and Pharmacy Practice General Administration – EDA	**Dr. Yasmeen Yehia** Manager of Clinical Pharmacy Unit at Drug Utilization and Pharmacy Practice General Administration-EDA
Under Supervision of	
Dr. Abeer Elbeheiry General Manager of Drug Utilization and Pharmacy Practice General Administration, EDA	
Dr. Shereen Abdel Gawad Head of Pharmaceutical Care Central Administration, EDA Head of Pharmacy Practice Guides and National Drug Lists Committee	

External Experts of the Pharmacy Practice Guides and National Drug Lists Committee- EDA (Ordered Alphabetically)	
Dr. Mary Gamal Roushdy Kirollos	Director of Medical Technology Administration - Unified Procurement Authority (UPA)
Dr. Mariam Soliman ElDebeiky	Manager of the Medical Technology Reassessment Department - Unified Procurement Authority (UPA)
Prof. Mohamed Alkassas	Professor and Head of Hepatology, Gastroenterology and Endoscopy Dept., Faculty of Medicine, Helwan Uni.
Prof. Mohamed Farag Alyamany	Professor of Pharmacology and Toxicology Faculty of Pharmacy - Cairo University
Prof. Mona Shcaalan	Vice Dean for Research and Postgraduate Studies - Professor of Clinical Pharmacy – Faculty of Pharmacy – Misr International University
Prof. Nirmeen Ahmed Sabry	Professor of Clinical Pharmacy – Faculty of Pharmacy - Cairo University – Medication Management Consultant
Dr. Sherif Kamal El Din	Chairman Consultant of Egypt Healthcare Authority for Pharmacy Affairs.

Abbreviations

ACS	Acute Coronary Syndrome
ACT	Activated Clotting Time
ALT	Alanine Aminotransferase
aPCC	Activated prothrombin complex concentrate
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
CAD	Coronary Artery Disease
CBC	Complete blood count
CrCl	Creatinine Clearance
DOAC	Direct Oral Anticoagulant
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
dTT	Diluted Thrombin Time
DVT	Deep Vein Thrombosis
Dw	Dry weight
FFP	Fresh Frozen Plasma
GIT	Gastrointestinal Tract
Hb	Hemoglobin
HDD-CKD	Hemodialysis-dependent chronic kidney disease
HIT	heparin-induced thrombocytopenia
HITT	Heparin-Induced Thrombocytopenia and Thrombosis
INR	International Normalised Ratio
LIC	Liver iron concentration
NDD/PDD-CKD	Non-dialysis-dependent, Peritoneal-dialysis-dependent chronic kidney disease
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NSTEACS	non-ST elevation acute coronary syndrome
NVAF	Non-Valvular Atrial Fibrillation
PAD	Peripheral Artery Disease
PCC	Prothrombin Complex Concentrate
PE	Pulmonary Embolism
P-gp	P-glycoprotein
SJS	Stevens-Johnson syndrome
SNRIs	Serotonin Norepinephrine Reuptake Inhibitors
SSRIs	Selective Serotonin Reuptake Inhibitors.
TAVR	Transcatheter Aortic Valve Replacement
TEN	Toxic Epidermal Necrolysis
TIA	Transient Ischemic Attack
UFH	Intravenous Unfractionated Heparin
ULN	Upper limit normal
VKA	Vitamin K Antagonists
VKDB	Vitamin K Deficiency Bleeding
VTE	Venous Thromboembolic Events

Antianemia, Iron preparations

Ferrous Fumarate

Generic Name	Ferrous Fumarate
Dosage Form/Strengths	Tablets: 200 mg (equivalent to 65.57mg elemental iron). Syrup: 140 mg/5ml (equivalent to 45mg elemental iron). And in combinations.
Route of Administration	Oral
Pharmacologic Category	Iron Preparations. ATC: B03AA02
Indications	• Prophylaxis and treatment of iron deficiency states. • For prophylaxis during pregnancy during second and third trimester (a combination with folic acid is recommended).
Dosage Regimen	**Adult dosing** **Iron deficiency anemia (**100 to 200 mg elemental iron daily**)** **Tablets**: 200 mg two to three times a day. **Syrup:** 10ml once or twice daily. **Prevention of iron deficiency (**60 to 120mg elemental iron daily**)** **Tablets**: 200 mg once or twice a day. **Syrup**: 10ml taken once daily. **N.B**. For elderly and pregnant women *during the second trimester onwards:* The adult dose is appropriate. **Children under 12 years (syrup)** **Treatment of iron deficiency** *Full term infants and young children*: 0.5ml/kg/day in 2 - 3 divided doses daily. Do not exceed 20ml daily. **Prevention of iron deficiency** *Full term infants and young children*: 0.5ml/kg/day in 2 - 3 divided doses daily. Do not exceed 20ml daily. *Premature infants:* 0.5ml/day in infants weighing up to 3kgs.
Dosage Adjustment	No dose adjustment needed.
Contra-Indications	• Hypersensitivity to the active substance or to any of the excipients. • Paroxysmal nocturnal hemoglobinuria. • Hemosiderosis, haemochromatosis. • Active peptic ulcer. • Repeated blood transfusions. • Regional enteritis and ulcerative colitis. Must not be used in anemias other than those due to iron deficiency.
Adverse Drug Reactions	**>10%** **Gastrointestinal**: Constipation, darkening of stools, nausea, stomach cramps, vomiting.

	1% to 10% **Gastrointestinal**: Dental discoloration, diarrhea, heartburn. **Genitourinary**: Urine discoloration.
Monitoring Parameters	No monitoring parameters needed.
Drug Interactions	***Risk X: Avoid combination*** Baloxavir, Marboxil, Dimercaprol, Levonadifloxacin, Unithiol. ***Risk D: Consider therapy modification*** Alpha-Lipoic Acid, Antacids, Bictegravir, Bisphosphonate Derivatives Cabotegravir, Cefdinir, Deferiprone, Dolutegravir, Eltrombopag, Elvitegravir, Entacapone, Ferric Hydroxide, Polymaltose Complex, Levodopa, Levothyroxine, Methyldopa, Penicillamine, Phosphate Supplements, Polyethylene Glycol-Electrolyte Solution, Quinolones, Raltegravir, Roxadustat, Tetracyclines, Trientine, Vadadustat.
Pregnancy and Lactation	**Pregnancy** Can be used during pregnancy if clinically indicated. Use during the first trimester should be avoided unless evidence of iron deficiency. While taking iron as prophylaxis during 2nd and 3rd trimester is acceptable. **Lactation** Can be used during lactation if clinically indicated.
Administration	**Oral administration** Administer with a full glass of water. Due to the risk of mouth ulcerations and tooth discolouration, tablets should not be sucked, chewed or kept in the mouth, but swallowed whole with water. N.B. Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	• **Duration of treatment** of uncomplicated iron deficiency anemia can be treated 3months after reversal of anemia (up to 6 months total). • Patients with **microcytic anemia** resistant to treatment with iron alone should be screened for Vitamin B_{12} or folate deficiency. • **Prolonged or excessive use** in children without medical supervision may lead to toxic accumulation. • Some **post-gastrectomy patients** have poor absorption of iron. • Caution is advised when prescribing iron preparations to individuals with a history of peptic ulcers. • **Overdose**: Early signs and symptoms include nausea, vomiting, abdominal pain and diarrhea. In more serious cases, cool peripheries, hypotension and metabolic acidosis. In serious cases there can be recurrence of vomiting and gastrointestinal bleeding, 12 hours after ingestion. Shock can result from hypovolemia or direct cardiotoxicity. Monitoring, whole bowel irrigation, adequate hydration and use of deferoxamine or sodium bicarbonate may be beneficial.
Storage	Store between 15-30^{0}C. N.B. Refer to manufacturer PIL if there are specific considerations.

Iron Carboxymaltose

<table>
<tr><th>Generic Name</th><th>Iron Carboxymaltose</th></tr>
<tr><td>Dosage Form/Strengths</td><td>Solution for I.V injection \Infusion: 500 mg/10 mL.</td></tr>
<tr><td>Route of Administration</td><td>IV</td></tr>
<tr><td>Pharmacologic Category</td><td>Iron Preparations</td></tr>
<tr><td>Indications</td><td>Treatment of iron deficiency anemia in
• Adult and pediatric patients 1 year of age and older where oral iron is ineffective or intolerable or there is a need for rapid iron delivery.
• Adult patients who have non-dialysis dependent chronic kidney disease.</td></tr>
<tr><td>Dosage Regimen</td><td>
Determination of the total iron need
<table>
<tr><th>HB</th><th colspan="3">Weight</th></tr>
<tr><th>g/dL</th><th>below 35 kg</th><th>35 kg to <70 kg</th><th>70 kg and above</th></tr>
<tr><td><10</td><td>30 mg/kg</td><td>1,500 mg</td><td>2,000 mg</td></tr>
<tr><td>10 to <14</td><td>15 mg/kg</td><td>1,000 mg</td><td>1,500 mg</td></tr>
<tr><td>≥14</td><td>15 mg/kg</td><td>500 mg</td><td>500 mg</td></tr>
</table>
Maximum doses:
Adults and adolescents aged 14 years and older
A single dose should not exceed:
• IV injection: 15 mg iron/kg.
• IV infusion: 20 mg iron/kg.
• The maximum recommended cumulative dose per week is 1,000 mg of iron.
Children and adolescents aged 1 to 13 years
A single dose per week should not exceed:
• 15 mg iron/kg body weight.
• 750 mg of iron.
N.B if higher doses are needed, administration of an additional dose should be a minimum of 7 days apart from the first dose.

Post-iron repletion assessments
The Hb level should be re-assessed after not less than 4 weeks post final administration to allow adequate time for erythropoiesis and iron utilization.

Patients with hemodialysis-dependent chronic kidney disease
Adults and adolescents aged 14 years and older
Single maximum daily dose: 200 mg.
</td></tr>
</table>

	Children and adolescents aged 1 to 13 years Efficacy and safety in this indication has not been established.
Dosage Adjustment	**Renal Impairment** Hemodialysis-dependent chronic kidney disease: No safety data for single doses of more than 200 mg iron. **Hepatic Impairment** • Hepatic dysfunction: Administered only after careful benefit/risk assessment with careful monitoring of iron status to avoid iron overload. • Hepatic dysfunction where iron overload is a precipitating factor, in particular Porphyria Cutanea Tarda (PCT): Avoid use.
Contra-Indications	• Hypersensitivity to the active substance or any of the excipients. • known serious hypersensitivity to other parenteral iron products. • Anemia not due to iron deficiency, e.g. other microcytic anaemia. • Iron overload or disturbances in the utilization of iron.
Adverse Drug Reactions	**>10%** **Endocrine & metabolic**: Hypophosphatemia (children, adolescents: 13%; adults: 1% to 2%). **1% to 10%** **Cardiovascular**: Flushing (≤4%), hypertension (1% to 4%), hypotension (≤1%), increased systolic blood pressure (6%). **Dermatologic**: Erythema of skin (≤3%), skin rash (children, adolescents: 8%; adults: 1%). **Gastrointestinal**: Dysgeusia (1%), gastrointestinal infection (children, adolescents: 3%), nausea (1% to 7%), vomiting (≤5%). **Hematologic & oncologic**: Decreased platelet count (children, adolescents: 3%), decreased white blood cell count (children, adolescents: 3%). **Hepatic**: Increased liver enzymes (1% to 3%). **Local**: Injection-site reaction (3% to 8%) **Nervous system**: Dizziness (1% to 2%), headache (children, adolescents: 5%; adults: 1%). **Respiratory**: Nasopharyngitis (children, adolescents: 3%).
Monitoring Parameters	• Iron status: Hemoglobin and hematocrit, reticulocyte count, serum ferritin, serum iron, prior to therapy re-assessed after not less than 4 weeks post final administration. • Monitor carefully for signs and symptoms of hypersensitivity during and after administration for at least 30 minutes. • Monitor for extravasation. • Serum phosphate in patients who receive multiple administrations at higher doses or long-term treatment, and those with risk factors for hypophosphatemia. Correct pre-existing hypophosphatemia prior to initiating therapy. • Monitor patients closely for signs and symptoms of hypertension.
Drug Interactions	***Risk X: Avoid combination*** Dimercaprol, Levonadifloxacin.

Pregnancy and Lactation	**Pregnancy** Limited data. No data for parentral iron in the first trimester. No safety concerns for use during second and third trimester. Can be used after evaluation of risk/benefit. Fetal bradycardia may occur. **Lactation** Limited data. It is unlikely to represent a risk to the breast-fed child.
Administration	**IV Administration** • Trained staff to evaluate and manage anaphylactic reactions should be immediately available. **Preparation of administration** Dilute with 0.9% m/V sodium chloride solution to concentration not less than 2 mg iron/mL. **Rate of infusion** • Dose 100-200mg diluted in 50 ml saline with no minimal prescribed time. • Dose: >200 to 500 mg diluted in 100ml administered in not less than 6 minutes. • Dose: >500 to 1,000 mg diluted in 250 ml administered in 15 minutes. N.B. Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	• **Hypersensitivity**: Severe and fatal anaphylactic reactions have been reported with sudden onset of respiratory difficulty or cardiovascular collapse. It may progress to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction). Observe for at least 30 minutes. If signs of hypersensitivity appeared, discontinue use immediately and administer appropriate therapy. Risk is higher in patients with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis) and in patients with known allergies including drug allergies or severe asthma, eczema patients. Use with caution. • **Extravasation**: Leakage at the injection site may lead to pain, inflammation and brown discoloration of the skin. Caution. If leakage occurred, therapy should be discontinued immediately. • **Hepatic impairment**: Use with extreme caution in patients with serious hepatic impairment. • **Acute or chronic infection**: Use with extreme caution. It is recommended that the administration of parentral iron is stopped in patients with bacteremia. • **Symptomatic Hypophosphatemia:** Monitor serum phosphate levels in patients at risk for low serum phosphate who require repeated course of treatment**.** Serious outcomes including osteomalacia and fractures may occur. In most cases, hypophosphatemia resolved within three months.
Storage	Store between 15-30 °C. Do not freeze. Store in the original package in order to protect from light. N.B. Refer to manufacturer PIL if there are specific considerations.

Iron Dextran

Generic Name	Iron Dextran
Dosage Form/Strengths	**Solution for I.M injection or I.V infusion:** 100mg/2ml (10%)
Route of Administration	IM, IV
Pharmacologic Category	Iron Preparations **ATC:** B05AA05
Indications	**Iron deficiency anemia in the following conditions** • Intolerance or ineffectiveness of oral iron preparations. • Clinical need for rapid iron delivery to iron stores e.g. blood loss.
Dosage Regimen	**N.B**. The total cumulative dose is determined by hemoglobin level and body weight. **Adults dosing** **Usual dose:** 100-200 mg, two or three times a week depending on the hemoglobin level. **Calculation of total dose** a) Iron deficiency Total dose in mg iron = (Body weight (kg) x (target Hb - actual Hb) (g/l) x 0.24) + storage iron (mg). **Or** Total dose in mg iron = Body weight in kg x (target Hb in mmol/l – actual Hb in mmol/l) x 3.84 + storage iron (mg). b) Iron replacement for blood loss Iron to be replaced [mg] = number of blood units lost x 200. **Or** Iron to be replaced [mg] = body weight (kg) x 0.24 x (target Hb in g/l - actual Hb in g/l). **Or** Iron to be replaced [mg] = body weight (kg) x 3.84 x (target Hb in mmol/l – actual Hb in mmol/l). **Notes** Use ideal body weight in kg; if actual body weight is less than IBW, use actual body weight. If the total necessary dose exceeds the maximum allowed daily dose, the administration has to be split. **Pediatrics** There is no documentation for efficacy and safety for use in children under 14 years.
Dosage Adjustment	**Renal Impairment** There are no dosage adjustments. Use with extreme caution. Acute renal failure: Contraindicated. **Hepatic Impairment** There are no dosage adjustments. Decompensated liver cirrhosis and hepatitis: Contraindicated.

Contra-Indications	• Hypersensitivity to Dextran or any component of the formulation. • Known serious hypersensitivity to other parenteral iron products. • Non-iron deficiency anemia (e.g. hemolytic anemia). • Iron overload or disturbances in utilization of iron (e.g. haemochromatosis, hemosiderosis). • Decompensated liver cirrhosis and hepatitis. • Acute or chronic infection, because parenteral iron administration may exacerbate bacterial or viral infections. • Acute renal failure (renal disease with severe oliguria or anuria).
Adverse Drug Reactions	**Frequency not defined** **Cardiovascular**: Bradycardia, cardiac arrhythmia, chest pain, chest tightness, flushing, hypertension, hypotension, shock, syncope, tachycardia. **Dermatologic**: Diaphoresis, pruritus, skin cyanosis, skin rash, urticarial. **Gastrointestinal**: Abdominal pain, diarrhea, dysgeusia, nausea, vomiting. **Genitourinary**: Hematuria. **Hematologic & oncologic**: Leukocytosis, lymphadenopathy, purpuric rash. **Hypersensitivity**: Anaphylaxis, type IV hypersensitivity reaction (large IV doses). **Infection**: Sterile abscess. **Local**: Atrophy at injection site (IM), fibrosis at injection site (IM), inflammation at injection site, injection site phlebitis (IV), local skin discoloration, local soreness/soreness at injection site (IM), pain at injection site (IM), swelling at injection site. **Nervous system**: Chills, disorientation, dizziness, headache, loss of consciousness, malaise, numbness, paresthesia, seizure, shivering, unresponsive to stimuli. **Neuromuscular & skeletal**: Arthralgia, arthritis, asthenia, back pain, exacerbation of arthritis, myalgia. **Respiratory**: Apnea, bronchospasm, dyspnea, wheezing. **Miscellaneous**: Fever. **Post marketing**: Hypersensitivity: Severe hypersensitivity reaction.
Monitoring Parameters	• Hypersensitivity reactions during and following each administration. • Iron status: Hemoglobin and hematocrit, reticulocyte count, serum ferritin, serum iron.
Drug Interactions	***Risk X: Avoid combination*** Dimercaprol, Levonadifloxacin ***Risk C: Monitor therapy*** Angiotensin-Converting Enzyme Inhibitors
Pregnancy and Lactation	**Pregnancy** No adequate human data. Studies in animals have shown reproductive toxicity. A careful risk benefit evaluation before use. **Lactation** There are no adequate data, it is preferable to not use during lactation.
Administration	**Preparation for IV administration** Dilute only in 0.9% NaCl or in D5%W. Not to be used if crystalline precipitate formed. It should not be administered concomitantly with

	other oral iron preparations • **IV infusion:** Doses of 100-200 mg may be diluted in 100 ml of diluents. • **IV injection:** Doses of 100-200 mg may be diluted in 10- 20 ml of diluents. **Administration** • **IV infusion:** The total amount of dose, up to 20 mg/kg bodyweight, is infused intravenously over 4 – 6 hours. First 25 mg of dose is infused over 15 minutes; when no adverse reactions occur continue the dose infusion at an infusion rate of not more than 100 ml in 30 minutes. • **IV injection:** Doses of 100 – 200 mg by slow intravenous injection (0.2 ml/min). First 25 mg of dose is injected slowly over 1 to 2 minutes, when no adverse reactions occur within 15 minutes continue the remain of dose. • **IM**: Undiluted injections of up to 100 mg iron (2.0 ml) given deep slowly into upper outer quadrant of the buttock, never into the arm or other exposed areas. N.B. Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	• **Hypersensitivity**: Severe and fatal anaphylactic reactions have been reported with sudden onset of respiratory difficulty or cardiovascular collapse. It may progress to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction). Observe for at least 30 minutes. If signs of hypersensitivity appeared, discontinue use immediately and administer appropriate therapy. Risk is higher in patients with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis) and in patients with known allergies including drug allergies or severe asthma, eczema patients. Use with caution. • **Delayed Reactions**: May occur with large intravenous doses. • **Rapid infusion**: Hypotensive episodes may occur if intravenous injection is administered too rapidly. • **Iron Overload**: Excessive therapy can lead to iatrogenic hemosiderosis. Do not administer to patients with iron overload. Periodically monitor hematologic and iron parameters. • **Appropriate use**: Not a substitute for blood or blood components. • **Hepatic impairment**: Use with extreme caution in patients with serious hepatic impairment. • **Rheumatoid arthritis**: Patients with rheumatoid arthritis may experience acute exacerbation of joint pain and swelling. • **Carcinogenicity**: The intramuscular injection of iron-carbohydrate complexes may be associated with an increased risk of carcinogenesis.
Storage	Store below 25°C; do not freeze. After dilution It should be used immediately. **N.B**. Refer to manufacturer PIL if there are specific considerations.

Iron Sucrose

Generic Name	Iron Sucrose
Dosage Form/Strengths	Solution for slow IV injection and infusion: 100mg elemental iron/5ml.
Route of Administration	*IV*
Pharmacologic Category	Iron Preparations ATC: B03AC
Indications	Treatment of iron deficiency in patients who cannot tolerate or benefit from oral preparations (e.g. active inflammatory bowel disease, chronic kidney disease). **N.B.** The diagnosis of iron deficiency must be based on appropriate laboratory tests (e.g. hemoglobin, serum ferritin, serum iron, etc.).
Dosage Regimen	**Adults dosing** **Usual dose:** 100-200 mg iron, one to three times a week depending on the hemoglobin level. Calculation of total dose for Iron deficiency **Total dose in mg iron** = (Body weight (kg) x (target Hb - actual Hb) (g/l) x 0.24) + storage iron (mg). **Below 35 kg BW body weight** Target Hb = 13 g/dL. Storage iron = 15 mg/kg BW **35 kg BW and above** Target Hb = 15 g/dL, Storage iron = 500 mg. **Pediatrics** Use has not been studied in children.
Dosage Adjustment	**Renal Impairment** No doasage adjustments are necessary. **Hepatic Impairment** There are no dosage adjustments available. Only be administered after careful risk/benefit assessment. Caution.
Contra-Indications	• Hypersensitivity to the active substance or any of the excipients. • Known serious hypersensitivity to other parenteral iron products. • Non-iron deficiency anemia (e.g. hemolytic anemia). • Iron overload or disturbances in utilization of iron (e.g. haemochromatosis, hemosiderosis).
Adverse Drug Reactions	**>10%** **Cardiovascular**: Hypotension (children, adolescents: 2%; adults: HDD-CKD: 39%, NDD/PDD-CKD: 2% - 3%). **Gastrointestinal**: Nausea (children, adolescents: 3%; adults: 5% - 15%). **Nervous system**: Headache (children, adolescents: 6%; adults: HDD-CKD: 13%, NDD/PDD-CKD: 3% - 4%).

	Neuromuscular & skeletal: Muscle cramps (HDD-CKD: 29%, NDD/PDD-CKD: ≤3%). **Respiratory**: Nasopharyngitis (≤16%) pharyngitis (≤16%), sinusitis (≤16%), upper respiratory tract infection (≤16%). **1% to 10%** **Cardiovascular**: Arteriovenous fistula site complication (thrombosis: children: 2%), chest pain (1% - 6%), heart failure (>1%), hypertension (children, adolescents: 2%; adults: 7% - 8%), peripheral edema (3% - 7%). **Dermatologic**: Pruritus (2% - 4%). **Endocrine & metabolic**: Hyperglycemia (3%), hypervolemia (1% to 3%), hypoglycemia (≤4%). **Gastrointestinal**: Abdominal pain (1% - 4%), diarrhea (5% - 8%), dysgeusia (≤8%), peritonitis (children: 4%), vomiting (children, adolescents: 4%; adults: 5% - 9%). **Infection**: Sepsis (>1%). **Local**: Infusion-site reaction (≤6%; including burning, infusion-site pain). **Nervous system:** Asthenia (≤3%), dizziness (≤4%). **Neuromuscular & skeletal**: Arthralgia (1% - 4%), back pain (1% - 2%), gout (3%), limb pain (3% - 6%), myalgia (1% - 4%). **Ophthalmic**: Conjunctivitis (≤3%). **Otic**: Otalgia (2%). **Respiratory**: Cough (children, adolescents: 4%; adults: 1% - 3%), dyspnea (1% - 6%), nasal congestion (1%), viral respiratory infection (children: 4%). **Miscellaneous**: Fever (children, adolescents: 4%; adults: ≤3%).
Monitoring Parameters	• Hypersensitivity reactions during and following each administration. • Iron status: Hemoglobin and hematocrit, reticulocyte count, serum ferritin, serum iron.
Drug Interactions	***Risk X: Avoid combination*** Bromperidol, Levonadifloxacin. ***Risk D: Consider therapy modification*** Amifostine, Obinutuzumab.
Pregnancy and Lactation	**Pregnancy** No data in the first trimester. No safety concerns for use during second and third trimester. Can be used after evaluation of risk/benefit. The unborn baby should be monitored for bradycardia during administration. **Lactation** Limited data. Low secretion of iron into the milk. Risk/benefit should be evaluated.
Administration	**IV Administration** *Intravenous drip infusion* Dilute immediately prior to infusion with 0.9% sodium chloride (NaCl) solution.

	<table><tr><th>Dose (mg of iron)</th><th>Maximum dilution volume of NaCl solution</th><th>Minimum Infusion Time</th></tr><tr><td>50 mg</td><td>50 ml</td><td>8 minutes</td></tr><tr><td>100 mg</td><td>100 ml</td><td>15 minutes</td></tr><tr><td>200 mg</td><td>200 ml</td><td>30 minutes</td></tr></table> *Intravenous injection* • **Slow IV injection**: administered as undiluted solution. Injection should not exceed 10 mL (200 mg iron). • **Rate of infusion:** 1 mL undiluted solution per minute. • May be injected directly into the venous line of the dialysis machine during a hemodialysis session. N.B. Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	• **Hypersensitivity**: Severe and fatal anaphylactic reactions have been reported with sudden onset of respiratory difficulty or cardiovascular collapse. It may progress to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction). Observe for at least 30 minutes. If signs of hypersensitivity appeared, discontinue use immediately and administer appropriate therapy. Risk is higher in patients with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis) and in patients with known allergies including drug allergies or severe asthma, eczema patients. Use with caution. • **Infusion reactions**: Leakage at the injection site may lead to pain, inflammation and brown discoloration of the skin. Caution. • **Hepatic impairment**: Use with extreme caution in patients with serious hepatic impairment. • **Acute or chronic infection**: Use with extreme caution. It is recommended that the administration of parentral iron is stopped in patients with bacteremia. • **Rapid infusion**: Hypotensive episodes may occur if intravenous injection is administered too rapidly.
Storage	Store below 25°C; do not freeze. After dilution It should be used immediately. N.B. Refer to manufacturer PIL if there are specific considerations

Antianemia, other

Cyanocobalamin

Generic Name	Cyanocobalamin (Vitamin B12)
Dosage Form/Strengths	Oily suspension for I.M injection: 1 mg/ml. Solution for I.M Injection: 1 mg/ml. Metered Nasal Spray: 0.5 mg. Sustained Release Capsule: 1 mg. Sublingual Tablet: 1 mg. Orally disintegrating Tablets: 1 mg. And in combinations.
Route of Administration	IM, Nasal, Oral.
Pharmacologic Category	Vitamin, Water Soluble. **ATC**: B03BA01
Indications	**Treatment of Vitamin B12 deficiency** which is dietary, drug-induced, or malabsorption, following partial gastrectomy, or strict vegetarianism. **Prevention of vitamin B12 deficiency** in patients with high needs of vitamin B12. **Prophylaxis and treatment of macrocytic anemias associated with vitamin B12 deficiency.** **Schilling test (injection form).**
Dosage Regimen	**Adult/Geriatric** **Vitamin B 12 deficiency** **Oral:** 50-150 mcg or more daily. **Nasal: initial:** 500 mcg weekly. Adjust dose according to serum B12 levels. **Treatment of pernicious anemia and other macrocytic anemias** • ***Without neurological involvement*** **Initially: IM** 250 to 1000 mcg on alternate days for 1-2 weeks, then 250 mcg weekly until the blood count is normal. **Oral**: 2000 mcg twice daily until full remission. **Maintenance: IM** 1000 mcg monthly or **Nasal Spray:** one spray (500 mcg) administered in one nostril once weekly, or **Oral:** 1,000 mcg once daily. • ***With neurological complications*** **Initially: IM** 1000 mcg on alternate days as long as improvement is occurring. **Maintenance:** 1000 mcg monthly or **Nasal Spray:** one spray (500 mcg) administered in one nostril once weekly, or **Oral:** 1,000 mcg once daily. **Prophylaxis of macrocytic anemia associated with Vitamin B12 deficiency** **IM:** 250 mcg – 1000 mcg monthly. **Schilling Test** **IM:** 1000 mcg.

	Dosing: pediatric **Vitamin B deficiency** **Oral:** 50 mcg daily. **Treatment of pernicious anemia and other macrocytic anemias** • ***Without neurological involvement*** **Initially: IM** 250 to 1000 mcg on alternate days for one to two weeks, then 250 mcg weekly until the blood count is normal. **Maintenance: IM** 1000 mcg monthly. • ***With neurological complications*** **Initially: IM** 1000 mcg on alternate days as long as improvement is occurring. **Maintenance:** 1000 mcg monthly. **Prophylaxis of macrocytic anemia associated with Vitamin B12 deficiency resulting** **IM:** 250 mcg – 1000 mcg monthly.
Dosage Adjustment	**Renal Impairment** There are no dosage adjustments needed. Some formulations may contain aluminum, which may accumulate in renal impairment. **Hepatic Impairment** There are no dosage adjustments needed.
Contra-Indications	▪ Hypersensitivity to cyanocobalamin (vitamin B12), cobalt, or any component of the formulation.
Adverse Drug Reactions	**>10%** ▪ **Central nervous system:** Headache (IM: 20%; intranasal: 4%). ▪ **Infection:** Infection (12% to 13%). ▪ **Neuromuscular & skeletal:** Asthenia (IM: 16%; intranasal: 4%). **1% to 10%** ▪ **Central nervous system:** Paresthesia (4%). ▪ **Gastrointestinal:** Glossitis (nasal: 4%), nausea (4%). ▪ **Respiratory:** Rhinitis (4% to 8%). **Frequency not defined** ▪ **Cardiovascular**: Cardiac failure, thrombosis (peripheral). ▪ **Dermatologic**: Pruritus, skin rash (transient). ▪ **Endocrine** & **metabolic**: Hypokalemia. ▪ **Gastrointestinal**: Diarrhea. ▪ **Hematologic** & **oncologic**: Polycythemia vera, thrombocythemia. ▪ **Hypersensitivity**: Anaphylactic shock (IM). ▪ **Respiratory**: Pulmonary edema. ▪ **Miscellaneous**: Swelling.
Monitoring Parameters	• Vitamin B12 levels and peripheral blood counts: 1 month after initiating therapy, then every 3-6 months thereafter. • Serum potassium levels periodically during therapy. • Platelet count periodically during therapy.

	• Folate and iron levels prior to treatment.
Drug Interactions	Chloramphenicol (Systemic): May diminish the therapeutic effect of Vitamin B12. *Monitor therapy.*
Pregnancy and Lactation	**Pregnancy** • There are no known risks with use during pregnancy. • Vitamin B12 requirements may be increased in pregnancy. • Vitamin B12 should not be used to treat megaloblastic anemia of pregnancy, unless Vitamin B12 deficiency has been demonstrated, because this is due to folate deficiency. **Lactation** • Vitamin B12 is found in breast milk but this is unlikely to harm the infant. • Vitamin B12 requirements may be increased in nursing women compared to non-breastfeeding women.
Administration	**Administration: IM** For IM administration only, do **not** administer IV. IM are preferred route of administration for children. **Administration: Oral** Administer on an empty stomach. Taken between meals. Some tablets are available for sublingual administration. **Administration: Intranasal** Administer 1 hour before or 1 hour after ingestion of hot foods/liquids. N.B. Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	▪ **Hypokalemia**: Hypokalemia, cardiac arrythmia and sudden death may occur in severe megaloblastic anemia which is treated intensely with vitamin B12. Monitor potassium level periodically. ▪ **Thrombocytosis**: May be caused by treatment of severe Vitamin B12 megaloblastic anemia. Monitor platelet count periodically. ▪ **Folic acid and iron levels**: should be monitored prior to therapy. If folate levels are low, folic acid should also be administered. Vitamin B12 doses >10 mcg daily may mask previously unrecognized folate deficiency. Administer iron concurrently if iron levels are low. All hematologic parameters should be normal when beginning treatment ▪ **Leber disease**: Patients with early Leber's disease (hereditary optic nerve atrophy) treated with vitamin B12 suffered severe and swift optic atrophy. ▪ **Polycythemia vera**: Vitamin B12 deficiency masks signs of polycythemia vera; Vitamin B12 administration may unmask this condition. Patients exhibiting clinical or hematologic response consistent with polycythemia vera should be referred for further evaluation. ▪ **Nasal spray use:** The effectiveness of nasal sprays in patients with nasal congestion, allergic rhinitis and upper respiratory infections is not established. Defer treatment with nasal spray until symptoms have cleared. ▪ **IV administration**: Avoid IV route; anaphylactic shock has occurred. ▪ **Hypersensitivity reactions**: Anaphylactic shock and death have been reported after parenteral vitamin B12 administration. Intradermal test dose of Vitamin B12 is recommended before administration for any patient suspected of cyanocobalamin hypersensitivity.

Storage	▪ **Injection:** Store below 25°C. Protect from light. ▪ **Intranasal spray:** Store between 15°C to 30°C; do not freeze. Protect from light. ▪ **Oral form:** Store between 15°C to 30°C. Protect from light and moisture. N.B. Refer to manufacturer PIL if there are specific considerations**.**

Folic Acid

Generic Name	Folic acid
Dosage Form/Strengths	**Tablet:** 0.5 mg, 0.8 mg, 1 mg, 5 mg. **Capsule:** 0.5 mg, 2.5 mg. **And in combinations as oral or injection form.**
Route of Administration	Oral.
Pharmacologic Category	Water soluble vitamin. **ATC:** B03BB01
Indications	• Treatment of megaloblastic anemia due to folate deficiency. • Prophylaxis of drug induced folate deficiency. • Prophylaxis against folate deficiency in chronic hemolytic states or in renal dialysis. • For the prevention of neural tube defects for woman planning a pregnancy and known to be at risk.
Dosage Regimen	**Dosing: Adults** • **Treatment of folate-deficient megaloblastic anemia**. Oral: 5 mg once daily for 4 months; doses up to 15 mg once daily for malabsorption states. Maintenance dose: 5mg every 1-7 days. • **In drug induced folate deficiency**. Oral: 5 mg once daily for 4 months; doses up to 15 mg once daily for malabsorption states. Maintenance dose: 5mg every 1-7 days. • **Prophylaxis in chronic hemolytic states or in renal dialysis** Oral 5mg every 1-7 days depending on diet and underlying disease. • **Pregnant women** ○ **Prophylactic dose in pregnancy** Oral: 0.4-0.5 mg daily prior to conception and be continued for at least the first 12 weeks of pregnancy**.** ○ **Prophylaxis in women with higher risk of neural tube defects** Oral: 5mg daily started before conception and continued throughout the first trimester. ○ **Pregnancy: In established folate deficiency** Oral**:** 5mg daily continued to term. **Dosing: Pediatric** • **In folate deficient megaloblastic anemia** Child 1-18 years: 5mg daily for 4 months; maintenance 5 mg every 1-7 days. • **In hemolytic anemia; metabolic disorders** Child 1-12 years: 2.5 mg-5 mg once daily. Child 12-18 years: 5-10 mg once daily. • **Prophylaxis of folate deficiency in renal dialysis** Child 1-12 years: 250 microgram/kg (max 10mg) once daily. Children 12-18 years 5-10 mg once daily.

	N.B. Parenteral route may be necessary for severe disease or if gastrointestinal absorption is impaired.
Dosage Adjustment	**Renal Impairment** There are no dosage adjustments. **Hepatic Impairment** There are no dosage adjustments.
Contra-Indications	• Hypersensitivity to folic acid or any component of the formulation. • Malignant disease unless megaloblastic anemia due to folate deficiency is an important complication. • Long-term folate therapy (3 months or longer) is contraindicated in any patient with untreated cobalamin deficiency. • Not to be given alone in the treatment of Addisonian pernicious anemia and other vitamin B12 deficiency states.
Adverse Drug Reactions	**Cardiovascular:** Flushing. **Central nervous system:** Malaise. **Dermatologic:** Erythema, pruritus, skin rash. **Hypersensitivity:** Hypersensitivity reaction. **Gastrointestinal disorders:** Anorexia, nausea, abdominal distension and flatulence. **Immune system disorders**: Allergic reactions, comprising erythema, rash, pruritus, urticaria, dyspnea. **Respiratory:** Bronchospasm.
Monitoring Parameters	There are no specific monitoring parameters.
Drug Interactions	***Risk X: Avoid combination*** Pafolacianine, Raltitrexed. ***Risk D: Consider therapy modification*** Pyrimethamine, Sulfadoxine.
Pregnancy And Lactation	**Pregnancy** No known hazards to folic acid use in pregnancy. Supplements of folic acid are often beneficial during pregnancy. **Lactation** No adverse effects have been observed in breast fed infants whose mothers were receiving folic acid.
Administration	• **Oral:** Use with or without meals. **N.B.** Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	• **Hydroxocobalamin deficiency**: Patients with vitamin B12 deficiency should not be treated with folic acid unless administered with adequate amounts of hydroxocobalamin, as it can mask the symptoms while the subacute irreversible damage to the nervous system will continue. • In undiagnosed megaloblastic anemia including in infancy, pernicious anemia or macrocytic anemia of unknown etiology: Folic acid should only be administered with adequate amounts of hydroxocobalamin.

	• **Folate dependent tumors**: Caution should be exercised when administering folic acid to patients who may have folate dependent tumors.
Storage	Store between (15°C to 30°C). Protect from light. **N.B.** Refer to manufacturer PIL if there are specific considerations

Hydroxocobalamin

Generic Name	Hydroxocobalamin
Dosage Form/Strengths	**Solution for I.M Injection:** 500mcg/ml, 1000mcg/2ml, 1000mcg/ml, 1500mcg/ml. And in combinations.
Route of Administration	IM
Pharmacologic Category	Vitamin, Water Soluble . **ATC:** B03BA03 B03BA53 (Hydroxocobalamin combinations)
Indications	• Treatment of Addisonian Pernicious anemia. • Prophylaxis and treatment of other macrocytic anemias associated with Vitamin B12 deficiency. • Treatment of Tobacco amblyopia. • Treatment of Leber's optic atrophy.
Dosage Regimen	**Dosing adults and pediatrics.** • **Addisonian pernicious anemias and other macrocytic anemias without neurological involvement.** **Initial: IM:** 250–1000 mcg every other day for duration of 1-2 weeks; after that, 250 mcg every week until the blood count returns to normal. **Maintenance: IM:** 1mg every two or three months • **Addisonian pernicious anemia and other macrocytic anemias with neurological involvement** **Initial: IM:** 1 mg every other day for as long as there is improvement. **Maintenance: IM:** 1mg every 2 months. • **Prophylaxis of macrocytic anemia associated with Vitamin B12 deficiency (resulting from gastrectomy, ileal resection, some malabsorption syndromes and strict vegetarianism)** **IM:** 1mg every 2-3 months. • **Tobacco amblyopia and Leber's optic atrophy** **Initially: IM:** 1mg or more daily by intramuscular injection for 2 weeks. Then twice weekly as long as improvement is occurring. **Maintenance: IM:** 1mg monthly.
Dosage Adjustment	**Renal Impairment** There are no dosage adjustments. **Hepatic Impairment** There are no dosage adjustments.
Contra-Indications	• Hypersensitivity to Hydroxocobalamin or any component of the formulation. • Hydroxocobalamin should not be used for the treatment of megaloblastic anemia of pregnancy unless vitamin B12 deficiency has been

	demonstrated.
Adverse Drug Reactions	**IM injection: Frequency not defined:** Dermatologic: Pruritus, skin rash (transient). Gastrointestinal: Diarrhea (mild, transient). Hypersensitivity: Anaphylaxis. Local: Pain at injection site. Miscellaneous: Swelling.
Monitoring Parameters	• Vitamin B12 levels and peripheral blood counts regularly to assure adequate therapy. • Serum potassium periodically during therapy. • Platelet counts during therapy, particularly in the first 48 hours of treatment. • Serum iron and folate prior to therapy.
Drug Interactions	No significant interaction.
Pregnancy and Lactation	**Pregnancy:** No adequate human data. Hydroxocobalamin injection should not be used for the treatment of megaloblastic anemia of pregnancy unless vitamin B12 deficiency has been demonstrated. **Lactation:** Hydroxocobalamin is present in breast milk. This is unlikely to harm the infant, and may be beneficial if the mother and infant are vitamin B12 deficient.
Administration	**Administration: IM** Administer solution by IM injection only. N.B. Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	▪ **Hypokalemia**: Hypokalemia, cardiac arrythmia and sudden death may occur in severe megaloblastic anemia. Monitor potassium level periodically. ▪ **Thrombocytosis**: May be caused by treatment of megaloblastic anemia. Monitor platelet count periodically. ▪ **Folic acid and iron levels**: should be monitored prior to therapy. If folate levels are low, folic acid should also be administered. Previously unrecognized folate deficiency may be masked.
Storage	▪ **Solution for IM injection**: Store between 15°C to 30°C. Protect from light. N.B. Refer to manufacturer PIL if there are specific considerations

Anticoagulants, Direct Thrombin inhibitors

Dabigatran

Generic Name	Dabigatran
Dosage Form/Strengths	**Capsules containing delayed Release Pellets**: 75 mg, 110 mg, 150 mg. **Capsules**: 75 mg, 110 mg, 150 mg.
Route of Administration	Oral
Pharmacologic Category	Anticoagulant, Direct Thrombin Inhibitor; Direct Oral Anticoagulant ATC: B01AE07
Indications	• Primary prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery. • Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension. • Treatment and prevention of recurrence of deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults. • Treatment and prevention of recurrence of VTE in pediatric patients from 8 years to less than 18 years of age.
Dosage Regimen	**Note:** Do not interchange dosage forms and do not combine more than one dosage form to achieve the total dose. There are differences between dosage forms due to different bioavailability. **Patients following orthopedic surgery in adults** **Oral: initial**: 110 mg (on the day of surgery 1-4 hours after completed surgery), then 220 mg daily. **Duration of maintenance dose**: 10 days following elective knee replacement surgery, and 28-35 days following elective hip replacement surgery. **Note**: If not started on the day of surgery, after hemostasis has been achieved initiate treatment with 220 mg once daily. **Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors.** **Oral**: 150 mg capsule twice daily. Duration should be individualized. **Treatment and prevention of recurrence of DVT and PE in adults.** **Oral**: 150 mg capsule twice daily following treatment with a parenteral anticoagulant for at least 5 days. Duration should be individualized. Short duration of therapy (at least 3 months) are considered for transient risk factors (e.g., recent surgery, trauma, immobilisation). Longer durations are considered for permanent risk factors or idiopathic DVT or PE.

Treatment of VTE and prevention of recurrent VTE in pediatric patients

Treatment should be initiated following treatment with a parenteral anticoagulant for at least 5 days.

Oral: Twice daily doses (with interval of 12 hours between doses) according to the following table. Duration should be individualized.

Weight /age combinations		Single dose in mg (to be taken twice)
Weight in kg	Age in years	
11 to <13	8 to <9	75
13 to <16	8 to <11	110
16 to <21	8 to <14	110
21 to <26	8 to <16	150
26 to <31	8 to <18	150
31 to <41	8 to <18	185
41 to <51	8 to <18	220
51 to <61	8 to <18	260
61 to <71	8 to <18	300
71 to <81	8 to <18	300
>81	10 to <18	300

Discontinuation of Dabigatran etexilate

Treatment should not be discontinued without medical advice. Patients should be instructed to contact the physician if they develop GIT symptoms such as dyspepsia.

Switching Dabigatran oral treatment to parenteral anticoagulant

It is recommended to wait till the time of the next dose.

Switching Parenteral anticoagulants to Dabigatran etexilate

After discontinuation parenteral anticoagulant, Dabigatran should be started 0-2 hours prior to the time of the next dose or at the time of discontinuation in case of continuous treatment (e.g. intravenous Unfractionated Heparin (UFH)).

Switching dabigatran etexilate treatment to Vitamin K antagonists (VKA)

Patients should start VKA 3 days before discontinuing dabigatran or 2 days in moderate renal impairment (CrCL ≥ 30-< 50 mL/min).

Switching VKA to dabigatran etexilate

	The VKA should be stopped. Dabigatran etexilate can be given as soon as the INR is < 2. ***Discontinuation due to Surgery and Other Interventions*** **Note:** Longer times may be considered prior to major surgery, spinal puncture, or placement of a spinal or epidural catheter or port where more complete hemostasis may be required. ***For Adults*** *CrCl ≥50 mL/minute:* Discontinue therapy 1-2 days before surgery. *CrCl <50 mL/minute:* Discontinue therapy 3-5 days before surgery. ***For pediatrics*** eGFR > 80 mL/min/1.73 m^2*:* Discontinue therapy 1 day before elective surgery. eGFR 50-80 mL/min/1.73 m^2: Discontinue therapy 2 days before elective surgery. eGFR 5< 50 mL/min/1.73 m^2: Dabigatran should not be used (has not been studied).
Dosage Adjustment	**Dosing adjustment for toxicity** Active pathological bleeding: Discontinue Dabigatran. Acute renal failure: Discontinue Dabigatran and consider alternative anticoagulant therapy. **Renal Impairment: Adult** • **Severe renal impairment (CrCl < 30 mL/min):** Contraindicated**.** • **Mild renal impairment:** No dose adjustment is necessary. • **Moderate renal impairment (CrCl 30-50 mL/min)** **Dose reduction is needed based on indications as follows** **Primary prevention of VTE in orthopedic surgery.** *Patients with moderate renal impairment (CrCl 30-50 mL/min), patients who receive concomitant verapamil, amiodarone, quinidine or patients aged 75 or above.* **Oral: Initial**: 75 mg (on the day of surgery 1-4 hours after completed surgery), then 150 mg daily. **Duration of maintenance dose**: 10 days following elective knee replacement surgery, and 28-35 days following elective hip replacement surgery. **Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors, Treatment and prevention of recurrence of DVT and PE in adults:** *Patients between 75-80 years **and** patients with moderate renal impairment (CrCl 30-50 mL/min) **or** patients with gastritis, esophagitis or gastroesophageal reflux, **and** other patients at increased risk of bleeding.* **Oral**: 300 mg or 220 mg daily. Selected dose depends on an individual assessment of the thromboembolic risk and the risk of bleeding.

	*Patients aged ≥80 years **and** Patients who receive concomitant verapamil.* **Oral***:* 110 mg capsule twice daily. **Renal Impairment: Pediatric** Pediatric patients with eGFR <50 mL/min/1.73m^2: Contraindicated. **Hepatic Impairment: Adult, Pediatrics** No dosage adjustments necessary. Elevated liver enzymes > 2 upper limit of normal (ULN): Not recommended due to lack of data.
Contra-Indications	• Serious hypersensitivity to dabigatran or any component of the formulation. • Active pathological bleeding. • Significant risk factor for major bleeding. • Patients with mechanical prosthetic heart valve(s). • Severe renal impairment (CrCl < 30 mL/minute) in adult patients. • eGFR <50 mL/min/1.73m^2 in pediatric patients. • Hepatic impairment expected to have any impact on survival. • Concomitant therapy with strong P-glycoprotein inhibitors (e.g., oral ketoconazole).
Adverse Drug Reactions	**>10%** • **Gastrointestinal**: Gastrointestinal signs and symptoms (25% to 40%). • **Hematologic and oncologic**: Hemorrhage (10% to 19%; major hemorrhage: ≤6%). **1% to 10%** • **Gastrointestinal**: Abdominal discomfort (≤8%), Abdominal discomfort (≤8%), Abdominal pain (≤8%), Dyspepsia (4% to 8%), Epigastric discomfort (≤8%), Esophagitis (≤3%), Gastritis (≤3%), Gastroesophageal reflux disease (≤3%), Gastrointestinal hemorrhage (≤7%; major: ≤3%), Hemorrhagic gastritis (≤3%), Upper abdominal pain (≤8%).
Monitoring Parameters	• Complete blood count (CBC). • Kidney functions prior to initiation, when clinically indicated, and at least annually. • Signs of bleeding. • Monitor patients frequently for signs and symptoms of neurological impairment in the context of epidural or spinal anesthesia/analgesia or lumbar puncture. • Anticoagulation effect may be measured. **Coagulation test thresholds at trough for adult patients that may be associated with an increased risk of bleeding.**

Test (trough value)	Thresold
dTT [ng/mL]	> 67
aPTT [x-fold upper limit of normal]	> 1.3

	INR: Should not be performed
Drug Interactions	***Risk X: Avoid combination*** Anticoagulants, Apixaban, Defibrotide, Dalteparin, Edoxaban, Enoxaparin, fondaparinux, Hemin, Lasmiditan, Mifepristone, Omacetaxine, Pacritinib, P-glycoprotein/ABCB1 Inducers, Rivaroxaban, Sparsentan, Taurursodiol, Urokinase, Vorapaxar, warfarin. ***Risk D: Consider therapy modification*** Antacids, Antiplatelet Agents (P2Y12 Inhibitors), Aspirin, Caplacizumab, Dronedarone, Erdafitinib, Ketoconazole (Systemic), Nonsteroidal Anti-Inflammatory Agents (Nonselective), Sodium Zirconium Cyclosilicate, Sotorasib, Ticagrelor.
Pregnancy and Lactation	**Pregnancy** • No adequate human data. Potential toxicity. Should not be used during pregnancy unless clearly necessary. • Patients should be switched to an alternative anticoagulant if pregnancy occurs during therapy. **Lactation** • No clinical data. Breastfeeding is not recommended during treatment with dabigatran, an alternate anticoagulant is suggested.
Administration	**Oral administration** Administer capsules with a full glass of water without regard to meals; however, if dyspepsia occurs, consider administration with meals. Do not break, chew, or open capsules, as this will lead to bleeding risk. **Missed dose** Take missed dose as soon as possible on the same day; skip missed dose if 6 hours before the next dose.
Warnings/ Precautions	**Bleeding** • The most common complication is bleeding, which can be severe and fatal. When severe bleedings occur, treatment must be discontinued and specific reversal agent is considered in adults. • Caution in conditions with an increased risk of bleeding which include: ○ Moderate renal impairment in adult. ○ Older patients (Moderate renal impairment in adult, particularly if they are underweight). ○ Co-administeration with P-gp inhibitor (e.g. Verapamil, amiodarone, quinidine or clarithromycin), platelet aggregation inhibitors such as clopidogrel, NSAIDs, SSRIs or SNRIs. ○ Congenital or acquired coagulation disorders. ○ Thrombocytopenia or functional platelet defects. ○ Recent biopsy, major trauma. ○ Bacterial endocarditis. ○ Esophagitis, gastritis or gastroesophageal reflux. The administration of a proton-pump inhibitor (PPI) can be considered to prevent GI bleeding.

Dabigatran reversal

- Idarucizumab is the most rapid specific antidote used in life-threatening or uncontrolled bleeding situations in adults but its efficacy and safety in pediatric patients have not been shown.
- Other possible options for adults include fresh whole blood or fresh frozen plasma, coagulation factor concentration (activated or non-activated), recombinant factor VIIa or platelet concentrates are other possible options.
- Consider administration of platelet concentrates in cases where thrombocytopenia is present or long-acting antiplatelet drugs have been used.
- Haemodialysis can remove dabigatran. However, its clinical use in treatment of bleeding is limited.

Antiphospholipid syndrome

Patients with a history of thrombosis who test positive for all three antiphospholipid antibodies (lupus anticoagulant, anticardiolipin, and anti-beta-2 glycoprotein I) may have a higher risk of recurrent thrombotic events than those who get Vitamin K antagonist medication. Use of dabigatran is not recommended in these patients.

Hepatic impairment

- Use in patients with moderate hepatic impairment (Child-Pugh class B) showed significant inter-subject variability, but no consistent change in exposure or pharmacodynamics was observed.
- Active liver disease patients were excluded from the randomized evaluation of long-term anticoagulant treatment.

Kidney impairment

- Before and during therapy, evaluate kidney function, especially if used in patients with any degree of preexisting renal impairment or in any condition that may result in a decline in kidney function.
- In any degree of renal impairment, dabigatran concentrations may rise, increasing the risk of bleeding.
- Serum concentrations in people with moderate impairment may be three times higher than in patients with adequate renal function.
- Stop therapy if a patient develops acute renal failure

Valvular heart disease

Use is not recommended in patients with valvular heart disease, including the presence of a bio-prosthetic heart valve; use is contraindicated in patients with mechanical prosthetic heart valves due to significant thromboembolic events and major bleeding.

Antithrombotic agents

- Due to an increased risk of bleeding, avoid use, if possible, with other direct thrombin inhibitors (e.g., Bivalirudin), Unfractionated heparin or Heparin derivatives, Low molecular weight heparins (e.g., Enoxaparin), Fondaparinux, thienopyridines (e.g., Clopidogrel), GPIIb/IIIa antagonists

	(e.g., Eptifibatide), Aspirin, Coumarin derivatives, Sulfinpyrazone, and Ticagrelor. • Use nonsteroidal anti-inflammatory medicines (NSAIDs) with caution. • Appropriate doses of unfractionated heparin may be used to maintain open central venous or arterial catheter or when UFH is given during catheter ablation for atrial fibrillation **Elderly** Risk of bleeding increases with age. Use with extreme caution or seek alternative treatment options. No dosage adjustment necessary unless kidney impairment coexists. **Surgeries** *Emergency surgery or urgent procedures*: Dabigatran etexilate should be temporarily discontinued. Idarucizumab may be used for rapid reversal of anticoagulation effect. *Subacute surgery/interventions:* Dabigatran etexilate should be temporarily discontinued. A surgery/intervention should be delayed if possible until at least 12 hours after the last dose. *Elective surgery*: If possible, Dabigatran etexilate should be discontinued at least 24 hours before invasive or surgical procedures. In patients at higher risk of bleeding or in major surgery where complete haemostasis may be required consider stopping Dabigatran etexilate 2-4 days before surgery. *Spinal anaesthesia/epidural anaesthesia/*lumbar *puncture*: Procedures may require complete haemostatic function. After removal of a catheter, an interval of at least 2 hours should elapse before the administration of the first dose of dabigatran etexilate. These patients require frequent observation for neurological signs and symptoms of spinal or epidural haematoma. *Postoperative phase*: Dabigatran etexilate should be restarted after the invasive procedure or surgical intervention as soon as possible if the clinical situation allows and adequate hemostasis has been established.
Storage	**Capsules**: Store between 15°C to 30°C. To avoid moisture, dispense, and store in the original package.

Anticoagulants, Heparins

Enoxaparin

Generic Name	Enoxaparin
Dosage Form/Strengths	**Solution for injection:** 20 mg (2,000 IU)/0.2ml, 40 mg (4,000 IU)/0.4ml, 60 mg (6,000 IU)/0.6ml, 80 mg (8,000 IU)/0.8ml, 100 mg/ml.
Route of Administration	*SC, IV*
Pharmacologic Category	Anticoagulant; Low Molecular Weight Heparin **ATC:** B01AB05
Indications	▪ **Prophylaxis of venous thromboembolic disease** ○ In moderate and high-risk surgical patients, especially those undergoing orthopedic or general surgery including cancer surgery. ○ In medical patients with an acute illness (such as acute heart failure, respiratory insufficiency, severe infections or rheumatic diseases) and reduced mobility at increased risk of venous thromboembolism. ▪ **Treatment of DVT and PE, excluding PE likely to require thrombolytic therapy or surgery.** ▪ **Extended treatment of DVT and PE and prevention of its recurrence in patients with active cancer.** ▪ **Prevention of thrombus formation in extra corporeal circulation during hemodialysis.** ▪ **Acute coronary syndrome:** ○ Treatment of unstable angina and non-ST-segment elevation myocardial infarction (NSTEMI), in combination with oral acetylsalicylic acid. ○ Treatment of acute ST-segment elevation myocardial infarction (STEMI) including patients to be managed medically or with subsequent percutaneous coronary intervention (PCI).
Dosage Regimen	**Adult/Geriatric** **Note:** For all indications except STEMI, no dose reduction is necessary in the elderly patients, unless kidney function is impaired. **Prophylaxis of venous thromboembolic disease** • ***Prophylaxis of deep-vein thrombosis in surgical patients of moderate risk:*** **SC**: Initial dose 20-40 mg given 2 hours prior surgery, then every 24 hours. Maintain treatment for at least 7-10 days whatever the recovery status (e.g., mobility). Continue prophylaxis until the patient no longer has significantly reduced mobility. • ***Prophylaxis of deep-vein thrombosis in medical patients, and surgical patients of High risk*:** (e.g. orthopaedic surgery): **SC**: 40 mg given 12 hours before surgery, then 40 mg every 24 hours. ○ For patients undergoing major orthopaedic surgery an extended thromboprophylaxis up to 5 weeks is recommended. ○ For patients with a high VTE risk who undergo abdominal or pelvic surgery for cancer an extended thromboprophylaxis up to 4 weeks

is recommended.

- ***Prophylaxis of venous thromboembolism in medical patients***

SC: 4,000 IU (40 mg) once daily. Treatment is prescribed for 6 to 14 days whatever the recovery status (e.g. mobility).

Treatment of venous thromboembolism and pulmonary embolism treatment.

SC: 150 IU/kg (1.5 mg/kg) once daily or as 100 IU/kg (1 mg/kg) twice daily. On average, treatment is prescribed for 7- 10 days. Oral anticoagulant therapy should be started when appropriate

The regimen selection is based on an individual's thromboembolic risk and of the risk of bleeding.

- 1.5 mg/kg regimen should be used in uncomplicated patients with low risk of VTE recurrence.
- 1 mg/kg twice daily regimen should be used in all other patients such as those with obesity, with symptomatic PE, cancer, recurrent VTE or proximal (vena iliaca) thrombosis.

In the extended treatment of DVT and PE and prevention of its recurrence in patients with active cancer

The individual thromboembolic and bleeding risks of the patient are carefully assessed.

SC: 1 mg/kg twice daily for 5 to 10 days followed by a 1.5 mg/kg once daily up to 6 months then reassess.

Prevention of thrombus formation during hemodialysis

Recommended dose: 1 mg/kg into the arterial line of the circuit at start of the session. This dose is sufficient for a 4-hour session; however, if fibrin rings are found, e.g., after a longer than normal session, a further dose of 0.5 to 1 mg/kg may be given.

If there is a high risk of hemorrhage: 0.5 mg/kg for double vascular access or 0.75 mg/kg for single vascular access.

Acute coronary syndromes

Note: Appropriate antiplatelet therapy such as oral acetylsalicylic acid (75 mg to 325 mg once daily) should be administered concomitantly unless contraindicated.

- ***Non-ST-elevation acute coronary syndromes***

SC: 1 mg/kg every 12 hours; usually for 2–8 days (minimum 2 days).

- ***Acute STEMI***
  - **Adult < 75 years:** Initially **IV** 30 mg, in addition to **SC:** 1 mg/kg for 1 dose, then **SC:** 1 mg/kg every 12 hours (max. dose for first two SC doses is 100 mg per dose) for up to 8 days or until hospital discharge, whichever comes first.

When administered in conjunction with a thrombolytic (fibrin

specific or non-fibrin specific), Enoxaparin sodium should be given between 15 minutes before and 30 minutes after the start of fibrinolytic therapy.

- **Adult ≥ 75 years:** an initial IV bolus must NOT be used. **SC** (0.75 mg/kg) every 12 hours (maximum 75 mg) for each of the first two SC doses only, followed by 0.75 mg/kg SC dosing for the remaining doses.

  N.B. No dose adjustment is necessary for other indications in geriatric patients unless kidney function is impaired.

- **For patients managed with PCI**, if the last dose of Enoxaparin sodium SC was given < 8 hours before balloon inflation, no additional dosing is needed. Otherwise, an IV bolus of 30 IU/kg (0.3 mg/kg) should be administered.

Switching with direct oral anticoagulants (DOAC)

For patients currently on Enoxaparin, discontinue Enoxaparin and start the DOAC 0 to 2 hours before the time of the next scheduled dose of Enoxaparin.

For patients currently receiving a DOAC, the first dose of enoxaparin sodium should be given at the time the next DOAC dose would be taken.

Pediatrics

The safety and efficacy of enoxaparin sodium in pediatric population have not been established.

Recommendations according to literature

Therapeutic regimen

Child 1 month: 1.5 mg/kg twice daily.
Child 2 months–17 years: 1 mg/kg twice daily**.**

Prophylactic regimen

Child 1 month: 0.75mg/kg twice daily**.**
Child 2 months–17 years: 0.5mg/kg twice daily; max. 40 mg per day.

Dosage Adjustment

Renal Impairment: Adult

Mild to moderate renal impairment (CrCl>30 mL/min): No dose adjustment is recommended.

Severe renal impairment (15-30 mL/min): Dosage adjustments as in the following table:

Indication	Dosing regimen
Prophylaxis of venous thromboembolic disease	2,000 IU (20 mg) SC once daily
Treatment of DVT and PE	100 IU/kg (1 mg/kg) body weight SC once daily

Extended treatment of DVT and PE in patients with active cancer	100 IU/kg (1 mg/kg) body weight SC once daily
Treatment of unstable angina and NSTEMI	100 IU/kg (1 mg/kg) body weight SC once daily
Treatment of acute STEMI (patients under 75)	1 x 3,000 IU (30 mg) IV bolus plus 100 IU/kg (1 mg/kg) body weight SC and then 100 IU/kg (1 mg/kg) body weight SC once daily
Treatment of acute STEMI (patients over 75)	No IV initial bolus, 75 IU/kg (0.75 mg/kg) body weight SC and then 75 IU/kg (0.75 mg/kg) body weight SC once daily.

End stage renal disease (CrCl < 15 mL/min): Use is not recommended (due to lack of data) except for the prevention of thrombus formation in extra corporeal circulation during hemodialysis.

Hepatic Impairment: Adult

There are no dosage adjustments (has not been studied); use cautiously due to increased risk of bleeding.

Contra-Indications

- Known hypersensitivity to Enoxaparin, heparin or its derivatives or any component of the formulation.
- History of immune mediated heparin-induced thrombocytopenia (HIT) in the last 100 days or in the presence of circulating antibodies.
- Active major bleeding and conditions with a high risk of hemorrhage.
- Spinal or epidural anesthesia or loco-regional anesthesia when Enoxaparin sodium is used for treatment in the previous 24 hours.

Adverse Drug Reactions

>10%

- **Hematologic and oncologic:** Anemia (≤16%), hemorrhage (4% to 13%).

1% to 10%

- **Cardiovascular:** Peripheral edema (6%).
- **Dermatologic:** Ecchymoses (3%).
- **Gastrointestinal:** Nausea (3%).
- **Genitourinary:** Hematuria (≤2%).
- **Hematologic and oncologic:** Major hemorrhage (≤4%; includes cases of intracranial [up to 0.8%], retroperitoneal, or intraocular hemorrhage, thrombocytopenia (≤3%).
- **Hepatic:** Increased serum alanine aminotransferase (>3 x ULN: 6%), increased serum aspartate aminotransferase (>3 x ULN: 6%).
- **Local:** Bleeding at injection site (3% to 5%), hematoma at injection site (9%), pain at injection site (2%).
- **Nervous system:** Confusion (2%).
- **Miscellaneous:** Fever (5% to 8%).

Monitoring Parameters	• CBC including platelet count prior to therapy and regularly during treatment. • Stool occult blood, signs and symptoms of bleeding. • Anti-factor Xa levels: as needed clinically as in bleeding. While it should be considered in renal impairmed patients. Anti-factor Xa activity: in pregnant women on therapeutic doses of enoxaparin and when using enoxaparin for the prevention of thromboembolism with mechanical heart valves. • Serum creatinine at baseline and during therapy. • Plasama potassium levels regularly. • Lumbar puncture/neuraxial anesthesia: Monitor patients frequently for signs and symptoms of neurological impairment (midline back pain, sensory and motor deficits, bowel and/or bladder dysfunction). **N.B**. Monitoring of activated partial thromboplastin time (aPTT), and activated clotting time (ACT) are not adequate for monitoring enoxaparin activity. **N.B.** In liver cirrhosis patients: Dose adjustment based on monitoring of anti-Xa levels is unreliable and not recommended
Drug Interactions	***Risk X: Avoid combination*** Apixaban, Dabigatran Etexilate, Defibrotide, Edoxaban, Hemin, Mifepristone, Omacetaxine, Rivaroxaban, Urokinase, Vorapaxar. ***Risk D: Consider therapy modification*** Agents with Antiplatelet Properties (e.g., P2Y12 inhibitors, NSAIDs, SSRIs, etc.), Caplacizumab, Desirudin, Dipyridamole, Nonsteroidal Anti-Inflammatory Agents.
Pregnancy and Lactation	**Pregnancy** No foetotoxicity or teratogenicity as shown by animal studies. Enoxaparin sodium should be used during pregnancy only if there is a clear need. Pregnant women receiving enoxaparin should be carefully monitored for evidence of bleeding or excessive anticoagulation and should be warned of the haemorrhagic risk. ***Lactation*** Can be used during breastfeeding. Passage of Enoxaparin or its metabolites in milk is very low. The oral absorption of Enoxaparin by baby is unlikely.
Administration	**Administration: IV:** ***STEMI and PCI only:*** ▪ Prepare a 30 mg bolus dose by expelling excess volume from a graduated prefilled syringe (e.g., the 40, 60, 80). ▪ May be diluted with neutral saline 9% or dextrose 5% immediately before use. Do not mix or co-administer with other medications. ▪ Enoxaparin sodium should be administered through an IV line. Flush IV access site with a sufficient amount of NS or D5W prior to and following IV bolus administration.

	▪ When used prior to PCI or as part of treatment for STEMI, a single dose may be administered IV except when the patient is ≥75 years of age and is experiencing STEMI then only administer by SC injection. **Administration SC** ▪ Administer by deep SC injection alternating between the left or right anterolateral and left or right posterolateral abdominal wall. May be self-administered. ▪ The whole length of the needle should be introduced vertically into a skin fold. The skin fold should not be released until the injection is complete. ▪ When the quantity of drug to be injected requires to be adjusted based on the patient's body weight, use the graduated pre-filled syringes to reach the required volume (or the nearest graduation) by discarding the excess before injection. ▪ Do not administer into bruised or scarred skin or through clothing. ▪ To minimize bruising, do not rub injection site. ▪ To avoid loss of drug from the prefilled syringes, do not expel the air bubble from the syringe prior to injection. Do not administer Enoxaparin intramuscularly. **Pediatrics**: For SC use only, do not administer IM or IV. **N.B.** Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	• **Biological agent**: To improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. • **Haemorrhage.** ○ Bleeding may occur at any site during treatment including fatal events, discontinue if bleeding occurs. Care should be taken in conditions with increased risk of hemorrhage. ○ Severe hemorrhage or overdosage may require protamine sulfate (1% solution) by slow infusion. Each mg of protamine sulfate neutralizes approximately 100 enoxaparin units if administered less than 8 hours before the protamine injection. Protamine 0.5mg is used if enoxaparine preceeds the antidote with more than 8 hours. After 12 hours of the enoxaparin sodium injection, protamine administration may not be required. • **Thrombocytopenia:** Monitor thrombocytopenia of any degree closely. If platelets significantly decreased during treatment (30 to 50 % of the initial value) or falled below 100,000/mm^3, enoxaparin must be immediately discontinued and if necessary, the patient switched to another non-heparin anticoagulant alternative treatment and evaluate for HIT and HITT. • **Risk of HIT with or without Thrombosis:** A serious antibody-mediated reaction caused by irreversible aggregation of platelets. This may lead to organ infarction, limb ischemia, or death. Monitor thrombocytopenia closely. • **Hyperkalemia**: Enoxaparin may suppress aldosterone production. Reversible hyperkalemia may occur, especially in patients with diabetes, renal impairment, history of metabolic acidosis, history of hyperkalemia,

	or taking concomitant potassium-sparing medication; Plasma potassium should be monitored regularly especially in patients at risk. • **Spinal/Epidural anaesthesia or lumbar puncture** must not be performed within 24 hours of administration of enoxaparin at therapeutic doses due to potentiality of neuraxial hematomas with symptoms of neurological impairment. • **Skin necrosis and cutaneous vasculitis** have been reported with LMWHs. If occurred, enoxaparin treatment should be discontinued. • **Mechanical prosthetic heart valves**: The use of enoxaparin has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves. Increased risk of thrombosis in pregnant women with mechanical prosthetic heart valves. Monitor more frequently and adjust dosage as needed. • **Elderly:** Careful clinical monitoring is advised and dose reduction might be considered in patients older than 75 years treated for STEMI. • **Renal impairment**: leads to higher exposure to enoxaparin which increases the risk of bleeding. In these patients, careful clinical monitoring is advised, and biological monitoring by anti-Xa activity measurement might be considered. Use is not recommended in end stage renal disease due to lack of data. • **Low weight:** Risk of bleeding may be increased in women <45 kg and in men <57 kg with prophylactic dosages (non-weight adjusted). • **Obese Patients** Obese patients (BMI >30 kg/m^2) are at higher risk for thromboembolism. Prophylactic doses have not been fully determined in these patients. Monitor carefully for signs and symptoms of thromboembolism. • **Conversion to other products**: Not to be used interchangeably (unit for unit) with other LMWHs. • **Percutaneous coronary revascularization:** To minimize bleeding risk after PCI, achieve hemostasis at the puncture site after PCI. If a closure device is used, sheath can be removed immediately. If manual compression is used, remove sheath 6 hours after the last IV/SC dose of Enoxaparin. Do not administer further doses until 6 to 8 hours after sheath removal; check for signs of bleeding/hematoma formation. • **Osteoporosis**: May occur following long-term administration (greater than 3 months. • **Serum aminotransferases elevations**: Significant elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels have occurred in patients who have received enoxaparin.
Storage	Store below 25°C. Do not freeze. N.B. Refer to manufacturer PIL if there are specific considerations

Heparin Calcium

Generic Name	Heparin Calcium
Dosage Form/Strengths	Solution for injection: 5000 I.U/0.5 mL.
Route of Administration	*SC, IV*
Pharmacologic Category	Anticoagulant ATC: B01AB01
Indications	• Prophylaxis of deep vein thrombosis and pulmonary embolism. • Treatment of deep vein thrombosis, pulmonary embolism, unstable angina pectoris and acute peripheral arterial occlusion. • Prophylaxis of mural thrombosis following myocardial infarction. • In extracorporeal circulation and hemodialysis.
Dosage Regimen	**Adult dosing** • **Prophylaxis of deep vein thrombosis and pulmonary embolism** **Initial**: SC: 5,000 units 2-hours prior to operation. Followed by: SC: 5,000 units every 8-12 hours, for 7-10 days or until the patient is fully ambulant. **Pregnant**: SC: 5,000-10,000 units every 12 hours, adjusted according to APTT or anti-Xa assay. • **Treatment of deep vein thrombosis and pulmonary embolism** **Loading dose:** IV: 5,000 units (10,000 unit in severe pulmonary embolism). **Maintenance**: **SC**: 10,000-20,000 units every 12 hours. or **IV infusion**: 1,000-2,000 units/hour. or **V injection**: 5,000-10,000 units every 4 hours. • **Treatment of unstable angina pectoris and acute peripheral arterial occlusion** **Loading dose: IV:** 5,000 units. **Maintenance:** **IV infusion:** 1,000-2,000 units/hour. or **IV injection**: 5,000-10,000 units every 4 hours. • **Prophylaxis of mural thrombosis following myocardial infarction** **SC**: 12,500 units every 12 hours for at least 10 days. • **In extracorporeal circulation and haemodialysis** ○ Cardiopulmonary bypass: **Initial**: IV: 300 units/kg, thereafter adjusted to maintain the activated clotting time (ACT) in the range 400-500 seconds. ○ Hemodialysis and hemofiltration: **Initial:** 1,000-5,000 units,

	Maintenance: 1,000-2,000 units/hour, adjusted to maintain clotting time >40 minutes. **Pediatric dosing** • **Treatment of deep vein thrombosis and pulmonary embolism** **Loading dose: IV:** 50 units/kg **Maintenance:** **SC**: 250 units/kg every 12 hours. or **IV infusion**: 15-25 units/kg/hour. or **V injection**: 100 units/kg every 4 hours. • **Treatment of unstable angina pectoris and acute peripheral arterial occlusion** **Loading dose: IV:** 50 units/kg **Maintenance:** or **IV infusion**: 15-25 units/kg/hour. or **V injection**: 100 units/kg every 4 hours.
Dosage Adjustment	**Elderly** Dose may need to be reduced. Monitoring of APTT may be recommended. **Renal Impairment** Caution. Risk of bleeding. Advanced renal disease: A reduction of dose may be necessary. **Hepatic Impairment** Caution. Risk of bleeding. Advanced hepatic disease: A reduction of dose may be necessary.
Contra-Indications	• Hypersensitivity to the active substance or to any of the other excipients. • Current or history of immune-mediated HIT. • An uncontrolled bleeding state, except when this is due to disseminated intravascular coagulation (menstruation is not a contra-indication). • Generalized or local hemorrhagic tendency. • Use of heparin for treatment rather than prophylaxis, in epidural anaesthesia (birth) or locoregional anaesthesia in elective surgical procedures may be considered contraindicated (risk of epidural or spinal haematoma resulting in prolonged or permanent paralysis). • In whom suitable blood coagulation tests cannot be performed at appropriate intervals.
Adverse Drug Reactions	**Postmarketing** **Dermatologic**: Transient alopecia. **Endocrine & metabolic**: Hyperkalemia, suppression of aldosterone synthesis. **Genitourinary**: Priapism. **Hematologic & oncologic**: Hemorrhage, thrombocytopenia, thrombosis in heparin-induced thrombocytopenia.

	Hypersensitivity: Anaphylactic shock, hypersensitivity reaction (including pruritus), infusion-related reaction (skin necrosis). **Local (subcutaneous)**: Erythema at injection site, hematoma at injection site, irritation at injection site, pain at injection site, skin ulceration at injection site, tissue necrosis at injection site. **Neuromuscular & skeletal**: Bone fracture, decreased bone mineral density, osteoporosis (with long-term use).
Monitoring Parameters	• CBC prior to therapy and regularly during treatment. • Level of anticoagulation can be monitored by anti-Factor Xa activity if needed in prophylaxis therapy**.** • APTT: baseline and daily laboratory monitoring, ideally at the same time each day (withdraw 4-6 hours after treatment initiation) is essential during full-dose Heparin treatment. • Dosage is considered adequate when the activated partial thromboplastin time (aPTT) is 1.5 to 2.5 times midpoint of normal range or control value. • Stool occult blood, signs and symptoms of bleeding. • Plasma potassium levels (initially and regularly if treatment is prolonged beyond 7 days). • Lumbar puncture/neuraxial anesthesia: Monitor patients frequently for signs and symptoms of neurological impairment (midline back pain, sensory and motor deficits, bowel and/or bladder dysfunction).
Drug Interactions	***Risk X: Avoid combination*** Alteplase, Andexanet Alfa, Apixaban, Corticorelin, Dabigatran, Defibrotide, Edoxaban, Hemin, Mifepristone, Omacetaxine, Oritavancin, Rivaroxaban, Streptokinase, Telavancin, Vorapaxar. ***Risk D: Consider therapy modification*** Antiplatelets, Caplacizumab, Desirudin, Dipyridamole, Ozagrel, Urokinase.
Pregnancy and Lactation	**Pregnancy:** Heparin does not cross the placenta. Evaluation of risk and benefit should be made before use. Due to the risk of uteroplacental hemorrhage, heparin should be stopped at the onset of birth. **Lactation:** Heparin does not appear in breast milk.
Administration	**Continuous intravenous infusion**: after dilution in 5% glucose or 0.9% sodium chloride. **Intermittent intravenous injection.** **Subcutaneous injection** N.B. Heparin should not be administered intramuscularly. **N.B.** Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	• **Thrombocytopenia:** It can occur mostly 5 to 9 days following the onset of heparin therapy. Treatment should be stopped immediately if platelet count falls below 100,000/mm^3 and, if necessary, administer an alternative anticoagulant and evaluate for HIT and HITT. • **HIT and Heparin-Induced Thrombocytopenia and Thrombosis (HITT):** A serious antibody-mediated reaction caused by irreversible aggregation of platelets can occur up to several weeks after discontinuation of heparin

	therapy. This may lead to organ infarction, limb ischemia, or death. Monitor platelet counts in patients receiving heparin treatment for longer than 5 days. • **Hyperkalemia**: Heparin may suppress aldosterone production. Reversible hyperkalemia may occur, especially in patients with diabetes, renal impairment, history of metabolic acidosis, history of hyperkalemia, or taking concomitant potassium-sparing medication; Monitor prior and regularly thereafter if treatment is prolonged beyond about 7 days. • **Spinal/Epidural anaesthesia or lumbar puncture:** Extreme care and monitoring if heparin used in the context of peri-dural or spinal anaesthesia due to risk of spinal or epidural hematoma and neurologic impairment. • **Heparin resistance:** Patients with altered Heparin responsiveness or resistance may require disproportionately higher doses of Heparin. Increased resistance occurs in fever, thrombosis, thrombophlebitis, infections with thrombosing tendencies, cancer and during pregnancy or the post-partum period. • **Hypersensitivity reactions:** Patients with documented hypersensitivity to Heparin should be given the drug only in clearly life-threatening situations. Heparin is derived from animal tissue; it should be cautiously used if there is a history of allergy. A trial dose of 1,000 I.U. may be given in patients with a history of allergy • **Osteoporosis:** May occur following long-term administration of high doses of Heparin (more than 10,000 I.U. per day of heparin over three months or longer). • **Elderly:** A higher incidence of bleeding has been reported in patients, particularly women, over 60 years of age. May require lower doses. • **Hemorrhage:** May occur, including fatal events, discontinue if bleeding occurs. Care should be taken in conditions with increased risk of hemorrhage. Severe hemorrhage or overdosage may require protamine sulfate (1% solution) by slow infusion. In any 10-minute period, no more than 50 mg should be administered, very slowly. Each mg of protamine sulfate neutralizes approximately 100 heparin units. Protamine dose varies according to the time of heparin administration and the dose administered. If more than 15 minutes have elapsed after heparin injection, lower doses of protamine will be needed.
Storage	• Store between 2-8^{0}C. Store in the original package. • Use immediately after opening. **N.B.** Refer to manufacturer PIL if there are specific considerations.

Heparin Sodium

Generic Name	Heparin sodium
Dosage Form/Strengths	**Solution for Injection/Infusion:** 1000 I.U./ml, 5000 I.U./1 ml.
Route of Administration	*IV, SC*
Pharmacologic Category	Anticoagulant **ATC:** B01AB01 (Parenteral)
Indications	• Prophylaxis of DVT and PE. • Treatment of DVT and PE. • Treatment of unstable angina pectoris and acute peripheral arterial occlusion. • Prophylaxis of mural thrombosis following myocardial infarction. • In extracorporeal circulation and haemodialysis. • Prevention of clotting in cardiac surgery.
Dosage Regimen	**Note:** Patients >60 years may have higher serum levels and clinical response (longer aPTTs). Dosage reduction and monitoring of aPTT may be advisable. **Note:** Preservative free formulations are recommended for neonates, infants, pregnant and lactating women. • **Prophylaxis of DVT and PE in adults.** **SC:** 5,000 units 2 hours pre-operatively, followed by 5,000 units every 8-12 hours, for 7-10 days or until the patient is fully ambulant. • **Treatment of DVT and PE.** **Adults** **Loading dose: IV:** 5,000 units (10,000 units may be used in severe pulmonary embolism). **Maintenance dose: IV infusion:** 1,000-2,000 units/ hour, or **SC**: 10,000-20,000 units every 12 hours, or **IV injection**: 5,000-10,000 units every 4 hours. **Pediatrics** **Loading dose: IV:** 50 units/kg. **Maintenance:** IV infusion: 15-25 units/kg/hour, or **SC**: 250 units/ kg every 12 hours, or **IV injection**: 100 units/ kg every 4 hours. • **Treatment of unstable angina pectoris and acute peripheral arterial occlusion.** **N.B.** Maintain an aPTT value 1.5-2.5 x midpoint of normal range or control value. Daily laboratory monitoring (ideally at the same time each day, starting 4-6 hours after initiation of treatment) is recommended. **Adults**

Loading dose: IV: 5,000 units.
Maintenance dose: IV infusion: 1,000-2,000 units/hour, or **IV injection:** 5,000-10,000 units every 4 hours.

Pediatrics

Loading dose: IV: 50 units/kg.
Maintenance: IV infusion: 15-25 units/kg/hour, or **IV injection**: 100 units/kg every 4 hours.

- **Prophylaxis of mural thrombosis following myocardial infarction in adults.**

  SC: 12,**500** units every 12 hours for at least 10 days.

- **In extracorporeal circulation and haemodialysis in adults.**

  Cardiopulmonary bypass: Initially IV 300 units/kg, then adjust dose to maintain the activated clotting time (ACT) in the range 400-500 seconds.

  Haemodialysis and haemofiltration: IV: 1,000-5,000 units initially, followed by infusion of 1,000-2,000 units/hour, adjusted to maintain clotting time > 40 minutes' maintenance.

- **Prevention of clotting in cardiac surgery.**

  Initial Dose: Not less than 150 units/ kg; adjust for longer procedures**.** Frequently, a dose of 300 units/kg is used for procedures estimated to last less than 60 minutes, or 400 units/kg for those estimated to last longer than 60 minutes.

Alternative dosing schedule (*Based on 68 kg patient. Adjust dose based on laboratory monitoring).*

Adults full dosing.

Deep Subcutaneous Injection

Initial Dose: IV: 5,000 units, followed by **SC**: 10,000 to 20,000 units.
Maintainance: SC: 8,000 to 10,000 units every 8 hours OR 15,000 to 20,000 units every 12 hours.

Intermittent Intravenous Injection

Initial dose: IV: 10,000 units, either undiluted or in 50 to 100 mL of 0.9% Sodium Chloride.
Maintainance: IV: 5,000 to 10,000 units, either undiluted or in 50 to 100 ml of 0.9% Sodium Chloride Injection, every 4 to 6 hours

Intravenous Infusion

Initial dose: IV injection: 5,000 units**.**
Continuous IV infusion: 20,000 to 40,000 units/24 hours in 1,000 mL of 0.9% Sodium Chloride Injection (or in any compatible solution).

Adults Low-Dose Prophylaxis of Postoperative Thromboembolism.

Initial: SC: 5,000 units 2 hours before surgery.

	Thereafter **SC**: 5,000 units every 8 to 12 hours for 7 days or until the patient is fully ambulatory, whichever is longer. **Pediatrics dosing.** **Initial: IV bolus** (over 10 minutes): 75 - 100 units/kg. **Maintenance** • Infants: 25 to 30 units/kg/hour; Infants < 2 months have the highest requirements (average 28 units/kg/hour). • Children > 1 year of age: 18 - 20 units/kg /hour. • Older children may require less heparin, similar to weight-adjusted adult dosage. **Monitoring** Adjust heparin to maintain aPTT of 60 to 85 seconds, anti-Factor Xa level of 0.35 to 0.70.
Dosage Adjustment	**Renal impairment** No initial dosage adjustments needed. Caution due to increased risk of bleeding. **Hepatic Impairment** No intial dosage adjustments needed. Caution.
Contra-Indications	• Hypersensitivity to the active substance or to any of the other excipients. • Current or history of immune-mediated HIT. • An uncontrolled bleeding state, except when this is due to disseminated intravascular coagulation (menstruation is not a contra-indication). • Generalized or local hemorrhagic tendency. • Use of heparin for treatment rather than prophylaxis, in epidural anaesthesia (birth) or locoregional anaesthesia in elective surgical procedures may be considered contraindicated (risk of epidural or spinal hematoma resulting in prolonged or permanent paralysis). • In whom suitable blood coagulation tests cannot be performed at appropriate intervals.
Adverse Drug Reactions	**Post marketing** ▪ **Cardiovascular:** Cardiac tamponade, vasospasm ▪ **Dermatologic:** Transient alopecia ▪ **Endocrine & metabolic:** Hyperkalemia, suppression of aldosterone synthesis ▪ **Genitourinary:** Priapism ▪ **Hematologic and oncologic:** Hemorrhage (including adrenal hemorrhage, ovarian hemorrhage, retroperitoneal hemorrhage), HIT, thrombocytopenia, thrombosis in HIT (including acute myocardial infarction, cerebral thrombosis, cerebrovascular accident, deep vein thrombosis, mesenteric thrombosis, peripheral gangrene, pulmonary embolism, renal artery thrombosis, skin necrosis) ▪ **Hepatic:** Increased serum alanine aminotransferase or aspartate aminotransferase

	▪ **Hypersensitivity:** Anaphylactic shock, hypersensitivity reaction (including pruritus and burning sensation of feet [plantar side]), infusion-related reaction (skin necrosis), nonimmune anaphylaxis ▪ **Local (SC):** Erythema at injection site, hematoma at injection site, irritation at injection site, pain at injection site, skin ulceration at injection site, tissue necrosis at injection site. ▪ **Neuromuscular and skeletal:** Bone fracture, decreased bone mineral density, osteoporosis (with long-term use)
Monitoring Parameters	▪ CBC including hematocrit, platelet count prior to therapy and regularly during treatment. ▪ Stool occult blood, signs and symptoms of bleeding. ▪ Level of anticoagulation can be monitored by anti-Factor Xa activity if needed in prophylaxis therapy**.** ▪ APTT: baseline and daily laboratory monitoring, ideally at the same time each day (withdraw 4-6 hours after treatment initiation) is essential during full-dose Heparin treatment. Dosage is considered adequate when the activated partial thromboplastin time (aPTT) is 1.5 to 2.5 times normal or when the whole blood clotting time is elevated approximately 2.5 to 3 times the control value. ▪ Plasama potassium levels (initially and regularly if treatment is prolonged beyond 7 days). ▪ Lumbar puncture/neuraxial anesthesia: Monitor patients frequently for signs and symptoms of neurological impairment (midline back pain, sensory and motor deficits, bowel and/or bladder dysfunction).
Drug Interactions	***Risk X: Avoid combination*** Andexanet Alfa (Coagulation Factor Xa [Recombinant], Inactivated), Apixaban, Corticorelin, Dabigatran Etexilate, Defibrotide, Edoxaban, Hemin, Mifepristone, Omacetaxine, Oritavancin, Rivaroxaban, Streptokinase, Telavancin, Urokinase, Vorapaxar. ***Risk D: Consider therapy modification*** Agents with Antiplatelet Properties (e.g., P2Y12 inhibitors, NSAIDs, SSRIs, etc.), Caplacizumab, Desirudin, Dipyridamole, Nonsteroidal Anti-Inflammatory Agents. **Note**: Careful clinical and biological monitoring is required when co-administered with other drugs affecting platelet function or the coagulation system, e.g. platelet aggregation inhibitors, thrombolytic agents, salicylates, NSAIDs, vitamin K antagonists, dextrans, activated protein C.
Pregnancy and Lactation	**Pregnancy** • Heparin does not cross the placenta. • Heparin can be used during all trimesters of pregnancy if clinically needed. • The use of Heparin in women with abortus imminens is contraindicated. • The use of a preservative-free formulation is recommended. **Lactation**

	• Heparin is not present in breast milk. • Heparin is considered acceptable for use in patients who are breastfeeding. • The use of preservative free products in lactating women patients is contraindicated.
Administration	**Administration: Subcutaneous** ▪ Inject in subcutaneous tissue. Injection sites should be rotated. Not all preparation intended for SC administration, verify product before use. **Administration: IV** ▪ **IV injection:** Should not exceed 15 mL. ▪ Do **not** administer IM because of pain, irritation, and hematoma formation. **Preparation for Administration** ▪ Determine concentration based on indication and dose. Use only if solution is clear. Do not use if solution is discolored or contains a precipitate. ▪ **Continuous IV infusion:** After adding Heparin to the infusion solution, invert the solution at least 6 times to adequately mix and prevent pooling of Heparin. ▪ Usual concentration for IV infusion: 100 units/mL of dextrose 5%, or neutral saline. **N.B.** Refer to manufacturer PIL if there are specific considerations**.**
Warnings/ Precautions	▪ **Thrombocytopenia:** It can occur 2 to 20 days (average 5 to 9) following the onset of heparin therapy. Treatment should be stopped immediately if platelet count falls below 100,000/mm^3 and, if necessary, administer an alternative anticoagulant and evaluate for HIT and HITT. ▪ **HIT and Heparin-Induced Thrombocytopenia and Thrombosis (HITT):** A serious antibody-mediated reaction caused by irreversible aggregation of platelets can occur up to several weeks after discontinuation of heparin therapy. This may lead to organ infarction, limb ischemia, or death. Monitor platelet counts in patients receiving heparin treatment for longer than 5 days. ▪ **Hyperkalemia**: Heparin may suppress aldosterone production. Reversible hyperkalemia may occur, especially in patients with diabetes, renal impairment, history of metabolic acidosis, history of hyperkalemia, or taking concomitant potassium-sparing medication; Monitor prior and regularly thereafter if treatment is prolonged beyond about 7 days. ▪ **Spinal/Epidural anaesthesia or lumbar puncture** Extreme care and monitoring if anticoagulants used in the context of peri-dural or spinal anaesthesia due to potentiality of neuraxial hematomas with symptoms of neurological impairment. ▪ **Heparin resistance:** Patients with altered Heparin responsiveness or resistance may require disproportionately higher doses of Heparin. Increased resistance occurs in fever, thrombosis, thrombophlebitis, infections with thrombosing tendencies, myocardial infarction, cancer and in postsurgical patients.

	▪ **Serum aminotransferases elevations:** Significant elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels have occurred in patients who have received heparin. ▪ **Hypersensitivity reactions:** Patients with documented hypersensitivity to heparin should be given the drug only in clearly life-threatening situations. Heparin is derived from animal tissue; it should be cautiously used if there is a history of allergy. ▪ **Osteoporosis:** May occur following long-term administration of high doses of Heparin. ▪ **Elderly:** A higher incidence of bleeding has been reported in patients, particularly women, over 60 years of age. May require lower doses. ▪ **Benzyl alcohol and derivatives:** Some dosage forms may contain benzyl alcohol as a preservative. IV administration of benzyl alcohol has been associated with serious adverse events and death in neonates ("gasping syndrome"). ▪ **Sulfites:** Some preparations contain sulfite which may cause allergic reactions. ▪ **Hemorrhage:** May occur, including fatal events, discontinue if bleeding occurs. Care should be taken in conditions with increased risk of hemorrhage. Severe hemorrhage or overdosage may require protamine sulfate (1% solution) by slow infusion. In any 10-minute period, no more than 50 mg should be administered, very slowly. Each mg of protamine sulfate neutralizes approximately 100 heparin units. Protamine dose varies according to the time of heparin administration and the dose administered.
Storage	Stored between 20° to 25°C. Do not freeze. Prepared infusion solution: may be kept for short time before use. Refer to leaflet. N.B. Refer to manufacturer PIL if there are specific considerations.

Anticoagulants, Direct Oral Anticoagulants

Apixaban

Generic Name	Apixaban
Dosage Form/Strengths	**Tablets** 2.5 mg, 5 mg
Route of Administration	Oral
Pharmacologic Category	Anticoagulant; Anticoagulant, Factor Xa Inhibitor; DOAC. **ATC code:** B01AF02
Indications	• Preventin of stroke and systemic embolism in patients with NVAF. • Prevention of VTE in patients who have undergone hip or knee replacement surgery. • Treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE.
Dosage Regimen	**Adult dosing.** • **Prevention of stroke and systemic embolism in patients with NVAF.** **Oral:** 5mg twice daily for long term. **Oral:** 2.5 mg twice daily in patients with NVAF and at least two of the following conditions: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL. • **Prevention of VTE: elective hip or knee replacement surgery.** Oral: 2.5 mg twice daily. The initial dose should be taken 12 to 24 hours after surgery 32 to 38 days (hip surgery) or 10-14 days (knee sugery). • **Treatment of DVT and PE.** Oral: 10 mg twice daily for the first 7 days followed by 5 mg twice daily. • **Prevention of recurrent DVT and PE.** Oral: 2.5mg twice daily following completion of 6 months of treatment with apixaban 5 mg twice daily or with another anticoagulant. **Pediatrics.** Safety and effectiveness in pediatric patients have not been established. **N.B.** The duration of overall therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding.
Dosage Adjustment	**Renal Impairment** • **Mild or moderate renal impairment:** Prevention of stroke and systemic embolism in patients with NVAF: No dose adjudtment except in case serum creatinine ≥ 1.5 mg/dL (133 micromole/L) associated with either age ≥ 80 years or body weight ≤ 60 kg: 2.5 mg twice daily. • **Severe renal impairment (creatinine clearance 15-29 mL/min):** Prevention of stroke and systemic embolism in patients with NVAF: 2.5 mg twice daily. Other indications; use with caution. **Hepatic Impairment**

	• **Mild, moderate impairment (Child-Pugh class A-B)**: No dosage adjustment required. Use with caution • **Severe impairment (Child-Pugh class C**): Use is not recommended. • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk: contraindicated.
Contra-Indications	• Active pathological bleeding. • Hypersensitivity to the active substance or to any of the excipients. • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk. • Risk factor for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial hemorrhage, known or suspected esophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities. • Concomitant treatment with any other anticoagulant agent.
Adverse Drug Reactions	**>10%** **Hematologic & oncologic:** Hemorrhage (≤ 15%; major hemorrhage: ≤ 2%; clinically relevant nonmajor hemorrhage: 4%). **1% to 10%** **Endocrine & metabolic:** Heavy menstrual bleeding (1%). **Gastrointestinal:** Gingival hemorrhage (≤1%), nausea (3%). **Genitourinary:** Hematuria (≤2%). **Hematologic & oncologic:** Anemia (3%), bruise (1% to 2%), hematoma (1% to 2%), rectal hemorrhage (≤1%). **Respiratory:** Epistaxis (≤4%), hemoptysis (≤1%).
Monitoring Parameters	• There is no need for routine monitoring of coagulation parameters. However, if clinically indicated, apixaban levels can be measured by calibrated quantitative anti-factor-Xa tests. • CBC including Hb count prior to therapy and regularly during treatment. • Stool occult blood, signs and symptoms of bleeding. • Kidney and hepatic function prior to initiation and periodically. • Lumbar puncture/neuraxial anesthesia: Monitor patients frequently for signs and symptoms of neurological impairment (midline back pain, sensory and motor deficits, bowel and/or bladder dysfunction).
Drug Interactions	***Risk X: Avoid combination*** Abciximab, Alteplase, Anticoagulants, Apalutamide, Dabigatran Etexilate, Defibrotide, Edoxaban, inducers of CYP3A4 (Strong) and P-glycoprotein, Hemin, Mifepristone, Omacetaxine, Rivaroxaban, St John's Wort, Streptokinase, Tenecteplase, Vorapaxar. ***Risk D: Consider therapy modification*** Antiplatelet Agents (P2Y12 Inhibitors), Aspirin, Caplacizumab, CYP3A4 Inducers (Strong), Fusidic Acid (Systemic), Inhibitors of CYP3A4 (Strong) and P-glycoprotein, Lenacapavir, Naproxen, Nonsteroidal Anti-Inflammatory

	Agents (Nonselective), Urokinase.
Pregnancy And Lactation	**Pregnancy** No data. Use is not recommended. **Lactation** No data. Women should be instructed either to discontinue breastfeeding or to discontinue Apixaban therapy, considering the importance of the drug to the mother.
Administration	**Administration: Oral** • Film-coated Tablets should be swallowed with water and may be taken without regard to food. **Missed dose** If a dose is missed, it should be taken as soon as possible on the same day. Twice daily dosing should be resumed. Do not double the dose to make up for a missed dose. **Crushing of tablets** • For patients unable to swallow whole tablets, apixaban tablets may be crushed and suspended in water, 5% Dextrose Injection, or apple juice, for prompt administration or for up to 4 hours. • Alternatively, tablets may be crushed and suspended in 60 mL of water or 5% Dextrose Injection and promptly delivered through a nasogastric tube. **N.B.** Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	**Hemorrhagic risk** Patients are to be carefully observed for signs of bleeding. Apixaban administration should be discontinued if severe haemorrhage occurs. Care should be taken in patients with an increased bleeding risk. Elderly patients and low weight patients (< 60 kg) have increased hemorrhagic risk. Caution. **Patients with Prosthetic Heart Valves** The safety and efficacy of Apixaban have not been studied in patients with prosthetic heart valves. Therefore, use is not recommended in these patients. **Acute PE in hemodynamically unstable patients or patients who require thrombolysis or pulmonary embolectomy** Apixaban is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who are hemodynamically unstable or who may receive thrombolysis or pulmonary embolectomy **Patients with antiphospholipid syndrome** Apixaban is not recommended for patients with a history of thrombosis who are diagnosed with triple positive antiphospholipid syndrome [positive for lupus anticoagulant, anticardiolipin, and anti-beta 2-glycoprotein I antibodies]) due to increased rates of recurrent thrombotic events. **Spinal/Epidural anaesthesia or lumbar puncture** Extreme care and

	monitoring if anticoagulants used in the context of peri-dural or spinal anaesthesia at therapeutic doses due to potentiality of neuraxial hematomas with symptoms of neurological impairment. **Premature discontinuation** Premature discontinuation of any oral anticoagulant in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. **Surgery and invasive procedures** Apixaban should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding while should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding. Apixaban should be restarted after surgery as soon as possible if the clinical situation allows and adequate hemostasis has been established. **Interaction with other medicinal products affecting hemostasis** The concomitant use of apixaban with antiplatelet agents increases the risk of bleeding. Care is to be taken if patients are treated concomitantly with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs), or non-steroidal anti-inflammatory medicinal products (NSAIDs), including acetylsalicylic acid. Following surgery, other platelet aggregation inhibitors are not recommended concomitantly with apixaban
Storage	Store between 15°C and 30°C. N.B. Refer to manufacturer PIL if there are specific considerations.

Rivaroxaban

Generic Name	Rivaroxaban
Dosage Form/Strengths	**Tablets** 2.5 mg, 10 mg, 15 mg, 20 mg **Orally disintegrating Tablets**:10mg, 15mg.
Route 0f Administration	Oral
Pharmacologic Category	Anticoagulant, Factor Xa Inhibitor; DOAC. **ATC code:** B01AF01
Indications	• In Nonvalvular atrial fibrillation to reduce risk of stroke and systemic embolism. • Treatment, prevention and reduction risk of recurrence of DVT or PE. • To reduce the risk of major atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers • To reduce the risk of major atherothrombotic events in patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events. • Treatment of VTE and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years. • Thromboprophylaxis in pediatric patients 2 years and older with congenital heart disease after the Fontan procedure.
Dosage Regimen	**Adult dosing** **N.B.** Duration of treatment should be individualized based on regular evaluations considering the risk for thrombotic events versus the bleeding risks**.** **Nonvalvular Atrial Fibrillation** Oral: 15 or 20 mg, once daily with food. **Treatment of DVT and/or PE** Oral: 15 mg orally twice daily with food for the first 21 days followed by 20 mg orally once daily with food for the remaining treatment. **Reduction in the Risk of Recurrence of DVT and/or PE** Oral: 10 mg once daily with or without food, after at least 6 months of standard anticoagulant treatment. A dose of Rivaroxaban 20 mg once daily may be considered in complicated comorbidities. **Prophylaxis of DVT Following Hip or Knee Replacement Surgery** Oral: 10 mg orally once daily with or without food starting 6- 10 hours after surgery once hemostasis has been established (for 12 days in knee replacement surgery and for 35 days in hip replacement surgery). **Prophylaxis of VTE in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding** **Oral**: 10 mg once daily, with or without food, in hospital and after hospital discharge for a total recommended duration of 31 to 39 days. **CAD or PAD** Oral: 2.5 mg orally twice daily with or without food, in combination with aspirin (75-100 mg) once daily.

ACS: Oral: 2.5 mg twice daily in combination with (75 - 100 mg) aspirin once daily with or without either a daily dose of 75 mg clopidogrel or a standard daily dose of ticlopidine.

Pediatric dosing

Treatment and prevention of VTE recurrence in children and adolescents.

Body weight from 30 to 50 kg:

Oral: 15 mg once daily. This is the maximum daily dose.

Body weight of 50 kg or more:

Oral: 20 mg once daily. This is the maximum daily dose.

Thromboprophylaxis in Pediatric Patients with Congenital Heart Disease after the Fontan Procedure.

Body weight of 50 kg or more:

Oral: 10 mg once daily.

Switching therapy

Converting from Vitamin K Antagonists (VKA) to rivaroxaban.

Prevention of stroke and systemic embolism:

VKA treatment should be stopped and Rivaroxaban therapy should be initiated once the INR is ≤ 3.0.

Treatment of DVT, PE and prevention of recurrence in adults and treatment of VTE and prevention of recurrence in paediatric patients:

VKA treatment should be stopped and rivaroxaban therapy should be initiated once the INR is ≤ 2.5.

N.B. INR values will be falsely elevated after the intake of Rivaroxaban.

Converting from rivaroxaban to Vitamin K antagonists (VKA).

VKA should be given concurrently until the INR is ≥ 2.0. For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing, as guided by INR testing.

Converting from parenteral anticoagulants to rivaroxaban.

Discontinue the parenteral anticoagulant and start rivaroxaban 0 to 2 hours before the time that the next scheduled administration of the parenteral anticoagulant (e.g. low molecular weight heparins) would be due or at the time of discontinuation of a continuously administered parenteral anticoagulant (e.g. intravenous unfractionated heparin).

Converting from rivaroxaban to parenteral anticoagulants.

Give the first dose of parenteral anticoagulant at the time the next rivaroxaban dose would be taken.

Dosage Adjustment

Renal Impairment

Mild impairment: No dose adjustments necessary.

Moderate and severe impairment (15 -49 ml/min) in adults.

- *For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation*: 15 mg once daily.
- *For the treatment of DVT and PE*: 15 mg twice daily for the first 3 weeks. Thereafter, 15 -20 mg once daily (after assessment of risk for bleeding and risk for recurrent DVT and PE).
- No dose adjustments necessary for 10 mg (or less) once daily.

Moderate and severe impairment (15 -49 ml/min) in Children and

	adolescents: Rivaroxaban is not recommended as no clinical data is available **CrCl < 15 ml/min (including patients on dialysis):** Not dialyzable: Avoid. **Dosing: Hepatic Impairment.** **Child-Pugh B and C hepatic impairment or hepatic disease associated with coagulopathy**: Avoid use. No clinical data are available in pediatric patients with hepatic impairment.
Contra-Indications	• Severe hypersensitivity reaction to active ingredient or any component of the formulation. • Active clinically significant bleeding. • Conditions of significant risk for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial hemorrhage, known or suspected esophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities. • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C. • Pregnancy and breast-feeding. • Concomitant treatment with any other anticoagulants except during switching or when heparin is given at doses necessary to maintain an open central venous or arterial catheter.
Adverse Drug Reactions	**>10%** • **Endocrine & metabolic:** Heavy menstrual bleeding (adolescents: 27%). • **Gastrointestinal:** Gastroenteritis (pediatric patients: 13%), vomiting (pediatric patients: 11% to 14%). • **Hematologic & oncologic:** Hemorrhage (pediatric patients and adults: 5% to 36%; major hemorrhage: ≤4%). • **Respiratory:** Cough (pediatric patients: 16%). **1% to 10%** • **Cardiovascular:** Syncope (1%). • **Dermatologic:** Pruritus (2%), skin blister (1%), skin rash (pediatric patients: 9%), wound secretion (3%). • **Gastrointestinal:** Abdominal pain (3%), gastrointestinal hemorrhage (2%). • **Hepatic:** Increased serum transaminases (>3 x ULN: 2%). • **Nervous system:** Anxiety (1%), depression (1%), dizziness (2%), fatigue (pediatric patients: 7%; adults: 1%), insomnia (2%). • **Neuromuscular & skeletal:** Back pain (3%), limb pain (pediatric patients and adults: 2% to 7%), muscle spasm (1%).
Monitoring Parameters	• There is no need for routine monitoring of coagulation parameters. However, if clinically indicated, rivaroxaban levels can be measured by calibrated quantitative anti-factor-Xa tests. • CBC including Hb count prior to therapy and regularly during treatment. • Stool occult blood, signs and symptoms of bleeding.

	• Kidney and hepatic function prior to initiation and periodically. • Lumbar puncture/neuraxial anesthesia: Monitor patients frequently for signs and symptoms of neurological impairment (midline back pain, sensory and motor deficits, bowel and/or bladder dysfunction).
Drug Interactions	***Risk X: Avoid combination.*** Abciximab, Alteplase, Anticoagulants, Apalutamide, Apixaban, Dabigatran Etexilate, Defibrotide, Edoxaban, Hemin, Inducers of CYP3A4 (Strong) and P-glycoprotein, Inhibitors of CYP3A4 (Strong) and P-glycoprotein (such as ketoconazole, itraconazole, voriconazole, posaconazole or ritonavir), Mifepristone, Omacetaxine, St John's Wort, Streptokinase, Tenecteplase, Vorapaxar. ***Risk D: Consider therapy modification.*** Antiplatelet Agents (P2Y12 Inhibitors), Aspirin, Caplacizumab, CYP3A4 Inducers (Strong), Enzalutamide, Fusidic Acid (Systemic), Inhibitors of CYP3A4 (Moderate) and P-glycoprotein, Lenacapavir, Nonsteroidal Anti-Inflammatory Agents (Nonselective), Urokinase.
Pregnancy and Lactation	**Pregnancy.** • Data are limited with rivaroxaban in pregnancy. • Rivaroxaban is considered contraindicated during pregnancy due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta. • Women of child bearing potential should avoid becoming pregnant during treatment with rivaroxaban. **Lactation.** • Rivaroxaban has been detected in human milk. Therefore, rivaroxaban is contraindicated during lactation.
Administration	**Oral administration.** • In higher doses (15 mg, 20 mg): Taken with food. Administer with the evening meal for once daily dosing. • In low doses (2.5mg, 10mg): Taken with or without food. **Missed dose:** the missed dose should be taken as soon as possible after it is noticed, but only on the same day. Otherwise, the patient should skip the dose and continue with the next dose as prescribed. **Crushing of tablets.** • Rivaroxaban tablets may be crushed and mixed with water or apple puree immediately prior to use and administered orally. • The crushed tablet may also be given through gastric tubes. N.B. Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	**Hemorrhagic risk** Patients are to be carefully observed for signs of bleeding. Rivaroxaban administration should be discontinued if severe haemorrhage occurs. Care should be taken in patients with an increased bleeding risk. **Patients with prosthetic valves** Rivaroxaban should not be used in patients having recently undergone

	transcatheter aortic valve replacement (TAVR). Not studied. **Patients with antiphospholipid syndrome.** Rivaroxaban is not recommended for patients with a history of thrombosis who are diagnosed with triple positive antiphospholipid syndrome [positive for lupus anticoagulant, anticardiolipin, and anti-beta 2-glycoprotein I antibodies]) due to increased rates of recurrent thrombotic events. **Patients with non-valvular atrial fibrillation who undergo PCI with stent placement:** Data on efficacy in this population are limited. **Hemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy** Safety and efficacy of rivaroxaban have not been established in these clinical situations. **Spinal/Epidural anaesthesia or lumbar puncture** Extreme care and monitoring if anticoagulants used in the context of peri-dural or spinal anaesthesia at therapeutic doses due to potentiality of neuraxial hematomas with symptoms of neurological impairment. There is no clinical experience with the use of 15 mg rivaroxaban in these situations. **Dermatological reactions** Serious skin reactions may occur within the first weeks of treatment. Rivaroxaban should be discontinued at the first appearance of a severe skin rash or any other sign of hypersensitivity in conjunction with mucosal lesions. **Premature discontinuation** Premature discontinuation of any oral anticoagulant in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from rivaroxaban to warfarin in clinical trials in atrial fibrillation patients. **Discontinuation for Surgery and other Interventions** If anticoagulation must be discontinued to reduce the risk of bleeding with surgical or other procedures, rivaroxaban should be stopped at least 24 hours before the procedure to reduce the risk of bleeding. Rivaroxaban should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established **Kidney impairment** Dose adjustment is necessary and specific adjustments are indication specific. Consider dose adjustment or discontinuation of rivaroxaban in patients who develop acute renal failure while on therapy.
Storage	Store between 15°C to 30°C. N.B. Refer to manufacturer PIL if there are specific considerations.

Anticoagulants, Vitamin K antagonists

Warfarin

Generic Name	Warfarin
Dosage Form/Strengths	**Tablet**: 1,2,3,5 mg
Route of Administration	Oral
Pharmacologic Category	Anticoagulant, Vitamin K Antagonist **ATC**: B01AA03
Indications	• Prophylaxis and treatment of venous thrombosis and pulmonary embolism. • Prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and/or prosthetic heart valves and vessels. . • Reduction in the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction.
Dosage Regimen	**Adult dosing** **Initial dosage** **Oral:** 2-10 mg, according to the patient's weight, age and general health. **Maintenance dose** Based on the effect of the initial dose on INR on day 3. Vary from less than 1.25 mg to 25 mg warfarin daily in some patients. **Usual maintainance dose: Oral**: 2-10 mg daily. **Pediatric dosing** **Initial**: 0.2mg/kg then adjust according to INR (similar to adults). Maintainance dose decreases with increasing age. **Elderly dosing** **Initial**: 2- 7.5 mg, which is then adjusted based on INR. **Notes**. • In adult patients having concomitant treatment with heparin or LMWH, it is possible to start with lower dose (2-7.5 mg warfarin per day) and to first check the INR value on days 3–4. • The entire daily dose should be taken at one time. • Effective prevention of thrombosis is generally only achieved after 5 days of treatment if the INR value has reached the recommended therapeutic level. • Monitor coagulation effect regularly. Warfarin has a narrow therapeutic window and its sensitivity varies from person to person and even within the same person. Sensitivity to warfarin increases with age and lower body weight, genetic factors, acquired causes such as heart failure or impaired hepatic function and other concomitant medication.

	• In acute cases, it is recommended that warfarin be combined with heparin to ensure a rapid anticoagulant effect. • Doses recommended for warfarin are general outlines and should be individualized depending on the condition being treated, local treatment guidelines, and the patient's ability to co-operate.
Dosage Adjustment	**Renal impairment** • No dose adjustments are required. • Moderate to severe renal impairment: Close monitoring of INR is required. Higher risk of bleeding. **Hepatic impaired functions** • Initial dose may need to be reduced due to enhanced warfarin effect. Close monitoring of INR is required. • Severe hepatic functions: Contraindicated. **Genetically abnormal enzyme types** Reduced initial and maintainance doses are recommended in the following conditions: • Patients with the alleles CYP2C9*2 or CYP2C9*3 in the enzyme CYP2C9 due to reduced metabolism of warfarin. It can also take longer to reach steady state for warfarin and its therapeutic effect. • Genetic differences in the gene VKORC1 that encodes the vitamin K epoxide reductase enzyme, the target of warfarin.
Contra-Indications	• Hypersensitivity to the active ingredient or to any of the excipients. • Hemorrhagic stroke. • Clinically significant bleeding. • Within 72 hours of major surgery with risk of severe bleeding. • Use of products containing St John's wort (Hypericum perforatum) and other drugs where interactions may lead to a significantly increased risk of bleeding. • Use during the first trimester and the last four weeks of pregnancy and within 48 hours postpartum. • Severely impaired hepatic function. • Unsupervised patients with conditions associated with potential high level of non-compliance • Patients at serious risk of haemorrhage, such as: Patients with haemorrhagic disorders, gastrointestinal, urogenital or respiratory bleeding tendency, oesophageal varices, arterial aneurysm, spinal puncture, peptic ulcer disease, severe wounds (including surgical wounds), bacterial endocarditis, malignant hypertension.
Adverse Drug Reactions	**<1%:** Dermatologic: Gangrene of skin and/or subcutaneous tissues, skin necrosis. **Frequency not defined** • Cardiovascular: Vasculitis. • Dermatologic: Bullous rash, dermatitis, pruritus.

	• Gastrointestinal: Abdominal pain, bloating, diarrhea, dysgeusia, flatulence, nausea, vomiting. • Hepatic: Hepatitis, increased liver enzymes. • Hypersensitivity: Anaphylaxis. • Nervous system: Chills.

Monitoring Parameters	• **INR monitoring**.
	  ○ During the first week: checked baseline and every day to every other day.
	  ○ Subsequently: once or twice a week until the patient is on the maintenance dose.
	  ○ Once a stable level is achieved: check every 4–6 weeks or sometimes longer periods.
	  ○ **The recommended normal target value** is INR 2.5 (± 0.5).
	  ○ In the case of treatment failures at normal treatment intensity and after complicated acute myocardial infarction: **The recommended target value** is INR 3 (± 0.5).
	  ○ Closer monitoring of INR during therapy is required in presence of parameters such as drug, herbal or food interaction, bleeding risk, hepatic and renal impairment, thyroid dysfunction, and genetic variation.
	• Haemoglobin levels and bleeding symptoms.
	• Renal and hepatic functions.
	• Consider genotyping of CYP2C9 and VKORC1 before initiation of therapy; however, routine genetic testing is not recommended.

Drug Interactions	***Risk X: Avoid combination.*** Abciximab, Alteplase, Defibrotide, Hemin, Mifepristone, Omacetaxine, Oxatomide, Streptokinase, Tenecteplase, Vorapaxar. ***Risk D: Consider therapy modification.*** Allopurinol, Amiodarone, Androgens, Barbiturates, Caplacizumab, Carbamazepine, Cholestyramine Resin, Cimetidine, CYP2C9 Inducers (Moderate), Desirudin, Fenofibrate and Derivatives, Fibric Acid Derivatives, Fluconazole, Fluorouracil Products, Fusidic Acid (Systemic), Ginkgo Biloba, Imatinib, Ivosidenib, Lornoxicam, Menatetrenone, Metronidazole (Systemic), Miconazole (Topical), Nafcillin, Nonsteroidal Anti-Inflammatory Agents (Nonselective), Rifamycin Derivatives, Salicylates, Sodium Zirconium Cyclosilicate, St John's Wort, Sulfonamide Antibiotics, Tamoxifen.
Pregnancy and Lactation	**Pregnancy** • Warfarin is contraindicated in the first trimester and during the last four weeks of pregnancy. Warfarin can cause severe malformations, fetal bleeding and fetal death. • Warafarin may be acceptable to use in mechanical heart valves patients who are at high risk for thromboembolism. **Lactation**

	• Warfarin is considered compatible with breastfeeding. Monitoring infants for bruising or bleeding is recommended.
Administration	**Administration: Oral** • Administer with or without food • Take at the same time each day. N.B. Refer to manufacturer PIL if there are specific considerations
Warnings/ Precautions	**Risk of hemorrhage:** Risk factors for bleeding include high intensity of anticoagulation (INR >4.0), age ≥65, highly variable INRs, history of gastrointestinal bleeding, uncontrolled hypertension, cerebrovascular disease, serious heart disease, risk of falling, anaemia, malignancy, trauma, renal insufficiency, concomitant drugs. More frequent INR monitoring and a shorter duration of therapy are needed. **Tissue necrosis**: Necrosis or gangrene of skin or other tissues can occur, with severe cases requiring debridement or amputation. Warfarin should be discontinued and alternative anticoagulant is considered if necessary. **Calciphylaxis**: A rare syndrome of vascular calcification with cutaneous necrosis, associated with high mortality. Discontinuation should be considered and appropriate treatment should be started. **Acute kidney injury** may occur during episodes of excessive anticoagulation and hematuria. Monitor renal functions. **Systemic atheroemboli and cholesterol microemboli**: Some cases have progressed to necrosis or death. Warfarin should be discontinued **HIT**: Initial therapy with warfarin in HIT has resulted in cases of amputation and death. Warfarin may be considered after platelet count has normalized. **Pregnant women with mechanical heart valves**: Warfarin may cause fetal harm; however, the benefits may outweigh the risks. **Interactions**: Many drugs and foods interact with warfarin. This warrants increased monitoring of the INR. Patients should be instructed to inform their doctor before they start to take any additional medications including over the counter medicines, herbal remedies or vitamin preparations. **Thrombophilia**: Patients with protein C deficiency are at risk of developing skin necrosis when initiating warfarin treatment. In patients with protein C deficiency therapy should be introduced without a loading dose.

	Overdose: Gastric lavage if justified. Treatment with activated charcoal (50 g for adults; 1g/kg for children) may be considered within one hour after ingestion of more than the patient's therapeutic dose. **Conditions may exaggerate the effect of warfarin**, and necessitate a reduction of dosage: loss of weight, acute illness (including infection), and cessation of smoking. **Conditions may reduce the effect of warfarin**, and require the dosage to be increased: weight gain, diarrhea and vomiting.
Storage	Store between 15°C to 30°C, Protect from light. N.B Refer to manufacturer PIL if there are specific considerations.

Anticoagulants, Other

Fondaparinux

Generic Name	Fondaparinux
Dosage Form/Strengths	**Solution in pre-filled syringe for S.C injection**: 7.5 mg/0.6ml **Solution in pre-filled syringe for S.C injection / IV injection or infusion**: 2.5mg/0.5ml.
Route of Administration	IV, SC
Pharmacologic Category	Anticoagulant, Factor Xa Inhibitor, Synthetic.
Indications	• Treatment of DVT and PE • Prophylaxis in patients undergoing major orthopaedic or abdominal surgery • Prophylaxis in medical patients who are at high risk for thromboembolic complications eg. cardiac insufficiency, acute respiratory disorders or acute infectious or inflammatory disease. • Treatment of adults with acute symptomatic spontaneous superficial-vein thrombosis of the lower limbs without concomitant deep-vein thrombosis.
Dosage Regimen	**Adult dosing** • **Treatment of DVT and PE** **SC**: according to body weight ○ Patients with body weight < 50 kg: 5mg daily. ○ Patients with body weight 50 to 100 kg: 7.5 mg daily. ○ Patients with body weight > 100 kg: 10 mg daily. **Duration**: Continue for at least 5 days and until adequate anticoagulation is established (INR: 2 to 3). Oral anticoagulant treatment (warfarin) should be started as soon as possible (within 72 hours). No data for duration beyond 10 days. • **Prophylaxis in patients undergoing major orthopedic or abdominal surgery** **SC**: 2.5 mg daily starting not less than 6 hours following surgical closure if hemostasis has been established. **Duration**: for 5 days up to 10 days. Patients with body weight < 50 kg: has not been studied. Caution. • **Prophylaxis in medical patients who are at high risk for thromboembolic complications** **SC**: 2.5 mg daily. **Duration:** for 6-14 days. Patients with body weight < 50 kg: has not been studied. Caution. • **Treatment of superficial-vein thrombosis** **SC**: 2.5 mg daily for 30 days and up to a maximum of 45 days in patients at high risk of thromboembolic complications. Patients with body weight < 50 kg: has not been studied. Use is not recommended.

	Pediatrics: No safety and efficacy data for use in in children below 17 years.
Dosage Adjustment	• **Renal impairment** ○ **Treatment of DVT and PE** ▪ CrCl >30 ml/min: No dosage adjustment is necessary. ▪ CrCl 30 to 50 ml/min: Patients with body weight > 100 kg: initial 10 mg daily then consider reduction to 7.5 mg. ▪ CrCl <30 ml/min: Use is not recommended. ○ **Prophylaxis of VTE or treatment of superficial vein thrombosis** ▪ CrCl >20 ml/min: No dosage adjustment is necessary. ▪ CrCl 20 to 50 ml/min: 1.5 mg once daily. Caution. ▪ CrC <20 ml/min: Use is not recommended. • **Hepatic impairment** ▪ Mild or moderate hepatic impairment: No dosing adjustment is necessary. ▪ Severe hepatic impairment: has not been studied. Caution. Use for treatment of superficial-vein thrombosis is not recommended.
Contra-Indications	• Hypersensitivity to the active substance or to any of the excipients. • Active major bleeding. • Acute bacterial endocarditis. • Severe renal impairment defined by creatinine clearance < 20 ml/min.
Adverse Drug Reactions	**>10%** **Hematologic & oncologic**: Anemia (2% to 20%). **1% to 10%:** **Cardiovascular**: Hypotension (≤4%). **Central nervous system**: Insomnia (≤5%), dizziness (≤4%), confusion (1% - 3%). **Dermatologic**: Increased wound secretion (≤5%), skin blister (≤3%). **Endocrine & metabolic**: Hypokalemia (≤4%). **Hematologic & oncologic**: Purpura (≤4%), thrombocytopenia (50,000 to 100,000/mm^3: 3%), hematoma (2% - 3%), minor hemorrhage (2% - 3%), major hemorrhage (1% - 3%), postoperative hemorrhage (≤2%). **Hepatic**: Increased serum ALT (>3 × ULN: 1% - 3%), increased serum AST (>3 × ULN: <1% - ≤2%). **Infection**: postoperative wound infection (abdominal surgery: 5%). **Respiratory**: Epistaxis (VTE: 1%).
Monitoring Parameters	• Rountinely monitor coagulation tests e.g. Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT). • CBC (Discontinue if the platelet count falls below 100,000/mm^3). • Serum creatinine level. • Stool occult blood test. • Monitor for signs and symptoms of bleeding.

Drug Interactions	***Risk X: Avoid combination*** Alteplase, Apixaban, Dabigatran Etexilate, Defibrotide, Edoxaban, Hemin, Mifepristone, Rivaroxaban, Streptokinase, Tenecteplase. ***Risk D: Consider therapy modification*** Antiplatelet Agents (P2Y12 Inhibitors), Aspirin, Caplacizumab, Desirudin, Glycoprotein IIb/IIIa Inhibitors, Nonsteroidal Anti-Inflammatory Agents (Nonselective), Ozagrel, Urokinase.
Pregnancy and Lactation	**Pregnancy**: Limited data. No evidence of adverse developmental outcomes in animal or human data. **Lactation**: Limited data. Oral absorption by the baby is unlikely.
Administration	**Subcutaneous administration** Deep subcutaneous injection at alternate sites. Do not expel the air bubble from the syringe before the injection. The whole length of the needle should be inserted perpendicularly. N.B Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	**Spinal or Epidural anaesthesia:** Extreme care and monitoring if anticoagulants used in the context of peri-dural or spinal anaesthesia at therapeutic doses due to potentiality of neuraxial hematomas with symptoms of neurological impairment. Spinal or epidural anaesthesia should not be used in patients receiving fondaparinux, for treatment of VTE rather than prophylaxis. Hematomas may result in long-term or permanent paralysis. **Hemorrhage:** Thrombocytopenia can occur. Caution in patients with high risk factor of bleeding. Agents that may increase risk of bleeding should not be administered concomitantly with fondaparinux. Elderly, patients with low body weight <50 kg and renal patients have higher risk of bleeding due to decreased elimination. **HIT:** Rare spontaneous reports of HIT in patients treated with fondaparinux have been received. Caution in patients with a history of HIT. **Renal impairment:** Dose adjustments may be needed. Contraindicated in severe renal impairment. **Severe hepatic impairment**: Caution for risk of bleeding due to a deficiency of coagulation factors.
Storage	Store between 15-30^{0}C. N.B Refer to manufacturer PIL if there are specific considerations.

Antihemophilia

Emicizumab

Generic Name	Emicizumab
Dosage Form/Strengths	Solution for S.C injection: 30 mg/ml, 105 mg/0.7ml, 60 mg/0.4 ml, 150mg/ml.
Route of Administration	SC
Pharmacologic Category	Antihemophilic Agent; Monoclonal Antibody ATC: B02BX06
Indications	Routine prophylaxis of bleeding episodes in patients (all age groups) with hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors.
Dosage Regimen	**Adult and Pediatric dosing** **Loading dose**: SC: 3 mg/kg once weekly for the first 4 weeks, followed by **Maintenance dose** **SC**: 1.5 mg/kg once every week, **or** **SC**: 3 mg/kg once every two weeks, **or** **SC**: 6 mg/kg once every four weeks. **Duration**: Intended for long-term prophylactic treatment. **N.B.** Different emicizumab concentrations (30 mg/mL and 150 mg/mL) should not be combined in the same syringe when making up the total volume. **N.B**. A volume greater than 2 mL per injection should not be administered.
Dosage Adjustment	**Renal Impairment** No doasgae adjustment is needed. Severe impairment: Not studied **Hepatic Impairment** No doasgae adjustment is needed. Severe impairment: Not studied.
Contra-Indications	Hypersensitivity to the active substance or to any of the excipients.
Adverse Drug Reactions	**>10%** **Local**: Injection-site reaction (22%, including bruising, discomfort, erythema, hematoma, induration, pruritus, pain, rash, swelling, urticaria). **Nervous system:** Headache (15%). **Neuromuscular & skeletal**: Arthralgia (15%). **1% to 10%** **Gastrointestinal**: Diarrhea (6%). **Immunologic**: Antibody development (5%). **Miscellaneous**: Fever (6%).

Monitoring Parameters	Monitor for thrombotic microangiopathy and thrombotic events if aPCC is administered with emicizumab. Laboratory tests for coagulation that can be used as they are unaffected by emicizumab: • Bethesda assays (bovine chromogenic) for FVIII inhibitor titers. • Thrombin time (TT). • One-stage, prothrombin time (PT)-based, single-factor assays. • Chromogenic-based single-factor assays other than FVIII. • Immuno-based assays (i.e., ELISA, turbidimetric methods). • Genetic tests of coagulation factors.
Drug Interactions	Activated prothrombin complex concentrate (aPCC): Laboratory testing and limitations of dose may be needed. Refer to Warnings/Precautions.
Pregnancy and Lactation	**Pregnancy**: No data. Should be used during pregnancy only if the potential benefit for the mother outweighs the risk to the fetus. **Lactation:** No data. Consider benefit and risk before discontinue breast-feeding or discontinue treatment.
Administration	**Subcutaneous use** The injection should be restricted to the recommended injection sites: the abdomen, the upper outer arms and the thighs. Alternating the site of injection may help prevent or reduce injection site reactions. N.B Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	**Biological product:** The name and the batch number of the administered product should be clearly recorded. **Bypassing agents:** Treatment with bypassing agents should be discontinued the day before starting emicizumab therapy. **Thrombotic Microangiopathy and thromboembolism associated with emicizumab and aPCC**: Thrombotic microangiopathy and thrombotic events were developed when on average a cumulative amount of >100 U/kg/24 hours of activated prothrombin complex concentrate (aPCC) was administered for 24 hours or more to patients receiving emicizumab prophylaxis. Patients receiving emicizumab should be monitored for the development of thromboembolism when administering with aPCC. The physician should immediately discontinue aPCC and interrupt emicizumab therapy if clinical symptoms, and/or laboratory findings consistent with thrombotic events occur, and manage as clinically indicated. Improvement was seen within one month. If aPCC is indicated in a patient receiving emicizumab prophylaxis, the initial dose should not exceed 50 U/kg and laboratory monitoring is recommended (including renal monitoring, platelet testing, and evaluation of thrombosis). **Immunogenicity**: Anti-emicizumab antibodies (including neutralizing

	antibodies) have developed in treated patients. In case of clinical signs of loss of efficacy, promptly assess the etiology and consider a change in treatment if neutralizing antibodies are suspected. **Laboratory Coagulation Test Interference**: Emicizumab interferes with activated clotting time (ACT), activated partial thromboplastin time (aPTT), and coagulation laboratory tests based on aPTT. Intrinsic pathway clotting-based laboratory tests should not be used.
Storage	• Store between 2°C to 8°C. Do not freeze. Protect from light. Do not shake. • Unopened vials can be kept at room temperature (below 30°C) for up to 7 days. N.B Refer to manufacturer PIL if there are specific considerations.

Factor Ⅷ

<table>
<tr><th>Generic Name</th><th>Factor VIII</th></tr>
<tr><td>Dosage Form/Strengths</td><td>Concentrate from human plasma: Powder for injection: 250 IU, 500 IU, 1000 IU.
Recombinant: Powder for injection: 250 IU, 500 IU, 1000 IU.</td></tr>
<tr><td>Route of Administration</td><td>IV</td></tr>
<tr><td>Pharmacologic Category</td><td>Antihemophilic Agent
ATC: B02BD02</td></tr>
<tr><td>Indications</td><td>Indicated in adults and children with hemophilia A (congenital Factor VIII deficiency) for:
• On-demand treatment and control of bleeding episodes.
• Perioperative management of bleeding.
• Routine prophylaxis to reduce the frequency of bleeding episodes.</td></tr>
<tr><td>Dosage Regimen</td><td>Adult and pediatric dosing
Required units = body weight (kg) × desired factor VIII rise (%) (IU/dl) × 0.5.

<u>On-demand Treatment</u>
<table>
<tr><th>Degree of hemorrhage/ Type of surgical procedure</th><th>Required factor VIII level (%) (IU/dl)</th><th>Frequency and Duration of therapy</th></tr>
<tr><td colspan="3">Hemorrhage</td></tr>
<tr><td>Minor
Early haemarthrosis, muscle bleeding or oral bleeding</td><td>20 - 40</td><td>Repeat every 12 to 24 hours. At least 1 day, until the bleeding is resolved or healing is achieved.</td></tr>
<tr><td>Moderate
More extensive haemarthrosis, muscle bleeding or haematoma</td><td>30 - 60</td><td>Repeat infusion every 12-24 hours until bleeding is resolved.</td></tr>
<tr><td>Major/Life-threatening
Life threatening haemorrhages</td><td>60 - 100</td><td>Repeat infusion every 8 to 24 hours until threat is resolved.</td></tr>
<tr><td colspan="3">Surgery</td></tr>
<tr><td>Minor
including tooth extraction</td><td>30 - 60</td><td>Every 24 hours, at least 1 day, until healing is achieved.</td></tr>
</table></td></tr>
</table>

	Major (intracranial, intraabdominal, intrathoracic, or joint-replacement)	80 – 100 (pre-and postoperative)	Repeat infusion every 8-24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dl).

Routine prophylaxis

Factor VIII

Adults and adolescents (≥12 years): Initial: 20 to 40 IU per kg administered 2 to 3 times weekly.

Children (<12 years): Initail: 25 to 50 IU per kg administered 2 to 3 times weekly. More frequent or higher doses may be required in children.

Dosage Adjustment

Renal Impairment

There are no dosage adjustments available.

Hepatic Impairment

There are no dosage adjustments available.

Contra-Indications

Hypersensitivity to the active substance or to any of the excipients.

Adverse Drug Reactions

Human

1% to 10%

Gastrointestinal: Abdominal pain (5%), nausea (5%).

Hematologic & oncologic: Increased factor VIII inhibitors (6%).

Local: Inflammation at injection site (2%).

Nervous system: Headache (≤5%), nervousness (10%), paresthesia (5%).

Ophthalmic: Blurred vision (5%).

Recombinant

>10%

Dermatologic: Pruritus (≤16%), skin rash (≤16%), urticaria (≤16%).

Hematologic & oncologic: Increased factor VIII inhibitors (previously untreated patients/minimally treated patients: 50% to 55%; previously treated patients: <1%; may include neutralizing antibodies).

Nervous system: Headache (9% to 24%).

Neuromuscular & skeletal: Arthralgia (5% to 23%).

Respiratory: Cough (10% to 13%), nasopharyngitis (12%), upper respiratory tract infection (7% to 22%).

Miscellaneous: Fever (9%; previously untreated patients/minimally treated patients: 30%; previously treated patents: 4%).

1% to 10%

Gastrointestinal: Abdominal distress (1%), abdominal pain (4%), diarrhea (5% to 8%), dyspepsia (2%), vomiting (3% to 8%).

Hypersensitivity: Hypersensitivity reaction (≤2%).

Infection: Varicella zoster infection (4%).

	Local: Infusion-site reaction (4% to 7%), injection-site reaction (1% to 3%). **Nervous system**: Asthenia (6%), chills (≤7%), dizziness (≤2%), insomnia (1% to 2%), malaise (1%), procedural pain (5%). **Neuromuscular & skeletal**: Back pain (4%), limb injury (6%), limb pain (≤4%). **Otic**: Otic infection (≤5%). **Respiratory**: Dyspnea (1%), lower respiratory tract infection (8%), nasal congestion (6%), pharyngitis (5%), pharyngolaryngeal pain (5%), rhinitis (8%).
Monitoring Parameters	• To guide dosing, appropriate determination of factor VIII levels is advised during the course of treatment using either a chromogenic assay (preferred) or a one-stage clotting assay. If the one-stage clotting assay is used, the result should be multiplied by a conversion factor of 2-2.5 to determine the patient's Factor VIII activity level. • Monitor for the development of Factor VIII inhibitors by appropriate clinical observations or laboratory tests. Perform a Bethesda inhibitor assay if expected plasma Factor VIII activity levels are not achieved, if bleeding is not controlled or following any product switch. Bethesda Units (BU) per ml of plasma is used.
Drug Interactions	There are no known significant interactions.
Pregnancy and Lactation	**Pregnancy and Lactation**: No data. Factor VIII should be used during pregnancy and lactation only if clearly indicated.
Administration	**Intravenous Administration** ▪ Refer to instructions in the manufacturer insert for reconstitution and preparation steps. ▪ Must not be mixed with other medicinal products for infusion. ▪ After reconstitution, infuse immediately or within 4 hours. Any unused product should be disposed. ▪ The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. **Rate of Infusion** Rate should be about 3ml/min. and not exceed 10 ml/min. N.B Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	**Biological Agent:** It is advised to record the name and batch number of the product. **Hypersensetivity:** Patients should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of chest, hypotension, and anaphylaxis. If symptoms develop, discontinuation immediately and administering appropriate treatment are recommended after contact with physician. **Neutralizing antibodies (inhibitors) to Factor VIII** may develop following administration. Highest risk occurs within the first 20 days and rarely, after the first 100 exposure days. If expected plasma Factor VIII activity levels are not achieved, or if bleeding is not controlled with an appropriate dose,

	perform an assay that measures Factor VIII inhibitor concentration. Also, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch. **Monitoring method**: If the one-stage clotting assay is used, the result should be multiplied by a conversion factor of 2-2.5 to determine the patient's Factor VIII activity level. **Human products**: The possibility of transmitting infective agents cannot be totally excluded despite measures taken. Vaccinations of hepatitis A and B should be considered.
Storage	• Do not store above 30 ºC. • Do not freeze. Protect from direct sunlight. N.B Refer to manufacturer PIL if there are specific considerations.

Factor IX

Generic Name	Factor IX
Dosage Form/Strengths	**Concentrate from human plasma**: 250 IU, 500 IU, 1000 IU, 1500 IU. **Recombinant**: 250 IU, 500 IU, 1000 IU.
Route of Administration	IV
Pharmacologic Category	Antihemophilic Agent ATC: B02BD04
Indications	Treatment and prophylaxis of bleeding in patients of all age groups with haemophilia B (congenital factor IX deficiency).
Dosage Regimen	**Adult and pediatrics** *On demand treatment* **Required units** =body weight (kg) x desired factor IX rise (%) or (IU/dl) x 0.85

Degree of hemorrhage/ Type of surgical procedure	Factor IX level required (%) or (IU/dl)	Frequency and Duration of therapy
Hemorrhage		
Minor Early haemarthrosis, muscle bleeding or oral bleeding	20 - 40	Repeat every 12 to 24 hours. At least 1 day, until bleeding episode as indicated by pain is resolved or healing is achieved.
Moderate More extensive hemarthrosis, muscle bleeding or hematoma	30 - 60	Repeat infusion every 24 hours for 3 to 4 days or more pain and acute disability are resolved.
Major/Life-threatening Life threatening haemorrhages	60 - 100	Repeat infusion every 8 to 24 hours until threat is resolved.
Surgery		
Minor surgery including tooth extraction	30 - 60	Every 24 hours, at least 1 day, until healing is achieved.
Major (intracranial, intraabdominal, intrathoracic, or joint-replacement)	80 – 100 (pre-and postoperative)	Repeat infusion every 8-24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor IX activity of 30% to 60% (IU/dl).

	Routine Prophylaxis **Adolescents/ adults ≥ 12 years**: 20 to 40 IU/kg at intervals 3 to 4 day (or 40 to 70 IU/kg twice weekly for previously treated patients). **Children < 12 years:** 35 to 75 IU/kg twice weekly for previously treated patients. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.
Dosage Adjustment	**Renal Impairment** There are no dosage adjustments available. **Hepatic Impairment** There are no dosage adjustments available.
Contra-Indications	Hypersensitivity to the active substance or to any of the excipients.
Adverse Drug Reactions	**Human** **Frequency not defined** **Cardiovascular**: Flushing, thrombosis. **Central nervous system**: Burning sensation (in jaw/skull), chills, headache, lethargy, paresthesia, rigors. **Dermatologic**: Skin photosensitivity, urticaria. **Gastrointestinal**: Diarrhea, nausea, vomiting. **Hematologic** & **oncologic**: Disseminated intravascular coagulation **Hepatic**: Increased serum alkaline phosphatase, increased serum ALT, increased serum AST. **Hypersensitivity**: Anaphylaxis, hypersensitivity reaction. **Local**: Discomfort at injection site (stinging, burning), injection site reaction, pain at injection site. **Neuromuscular & skeletal**: Neck tightness. **Ophthalmic**: Visual disturbance. **Respiratory**: Allergic rhinitis, asthma, laryngeal edema, pulmonary disease. **Miscellaneous**: Fever (including transient fever following rapid administration). **Recombinant** **>10%** **Immunologic**: Antibody development (2% to 30%). **Nervous system**: Headache (2% to 11%). **1% to 10%** **Cardiovascular**: Chest tightness (2%), flushing (3%). **Dermatologic**: Pruritic rash (1%), skin rash (2% to 6%), urticaria (3% to 5%). **Gastrointestinal**: Dysgeusia (1% to 5%), nausea (6%), vomiting (2%). **Hematologic & oncologic**: Factor IX inhibitor in hemophilia B (2% to 3%). **Hypersensitivity**: Hypersensitivity reaction (1%). **Infection**: Influenza (1%). **Local**: Cellulitis at injection site (2%), discomfort at injection site (1%),

	injection site phlebitis (2%), injection site reaction (2% to 8%), pain at injection site (6%). **Nervous system**: Apathy (1%), asthenia (1%), chills (2%), depression (1%), dizziness (8%), drowsiness (2%), lethargy (1%), tremor (2%). **Neuromuscular & skeletal**: Limb pain (1%). **Ophthalmic**: Blurred vision (2%). **Renal**: Renal infarction (2%). **Respiratory**: Dry cough (2%), dyspnea (3%), hypoxia (2%). **Miscellaneous**: Fever (3%).
Monitoring Parameters	• To guide dosing, appropriate determination of factor IX activity levels is advised during the course of treatment. N.B. When using an in vitro thromboplastin time (aPTT)-based one stage clotting assay, results can be significantly affected by both the type of aPTT reagent and the reference standard used in the assay. • Monitor for the development of Factor IX inhibitors by appropriate clinical observations or laboratory tests. Perform a Bethesda inhibitor assay if expected plasma Factor IX activity levels are not achieved, if bleeding is not controlled or following any product switch. Bethesda Units (BU) per ml of plasma is used.
Drug Interactions	There are no known significant interactions.
Pregnancy and Lactation	**Pregnancy and Lactation**: No data. Factor IX should be used during pregnancy and lactation only if clearly indicated.
Administration	**Intravenous Administration** • Refer to instructions in the manufacturer insert for reconstitution with diluent provided and preparation steps. • Must not be mixed with other medicinal products for infusion. • The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. • Infuse reconstituted solution immediately or within 3 hours of storage at room temperature after reconstitution **Rate of Infusion** Rate about 3 ml/minute not exceeding 10 mL per minute. N.B Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	**Biological Agent:** It is advised to record the name and batch number of the product. **Hypersensetivity:** Patients should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of chest, hypotension, and anaphylaxis. If symptoms develop, discontinuation immediately and administering appropriate treatment are recommended after contact with physician.

	Cardiovascular events: In patients with existing cardiovascular risk factors, administration of factor IX may increase the cardiovascular risk. **Thromboembolism:** Potential risk. Monitor for early signs of thromboembolism during therapy to patients with liver disease, fibrinolysis, peri-operative status, or risk for thromboembolic events or disseminated intravascular coagulation. **Nephrotic syndrome** has been reported in hemophilia B patients with factor IX inhibitors and a history of allergic reaction. **Human products**: The possibility of transmitting infective agents cannot be totally excluded despite measures taken. Vaccinations of hepatitis A and B should be considered.
Storage	• Store between 2°C to 8°C. • Do not freeze. Protect from light. • Can be stored up to 3 months at 25°C. Not to be refrigerated again. N.B Refer to manufacturer PIL if there are specific considerations.

Antihemorrhagics

Phytomenadione

Generic Name	Phytomenadione (Phytonadione) (Vitamin K_1)
Dosage Form/Strengths	**Solution for IM, slow IV injection or infusion:** 10 mg/ml **Lyophilized Powder:** 2 mg/0.2 ml, 10 mg/ml **Tablets:** 5 mg, 10 mg **Chewable Tablets:** 10 mg **Soft Gelatin Capsule:** 1 mg And in combinations.
Route of Administration	IM, IV, Oral.
Pharmacologic Category	Vitamin, Fat Soluble **ATC:** B02BA01
Indications	• Antidote to anticoagulant drugs of the coumarin type in the treatment of hemorrhage or threatened hemorrhage, associated with a low blood level of prothrombin or factor VII. • **Hypoprothrombinemia** secondary to: o Antibacterial therapy. o Administration of salicylates (interfere with vitamin K metabolism). o Factors limiting absorption or synthesis of vitamin k, e.g., obstructive jaundice, biliary fistula, sprue, ulcerative colitis, celiac disease, intestinal resection, cystic fibrosis of the pancreas, and regional enteritis. • Prophylaxis and treatment of vitamin k-deficiency bleeding in neonates.
Dosage Regimen	**Dosing: Adult** **Antidote to anticoagulant drugs of the coumarin type** **Oral:** Initial 2.5 to 10 mg (up to 25 mg, Rarely 50 mg). Repeat the dose if no satisfactory shortening of prothrombin time in 12 to 48 hours following oral administration. **For severe hemorrhage** **IV, IM:** 2.5 mg to 10 mg or more. Up to 25-50 mg may be administered as a single dose. Withdraw the coumarin anticoagulant. IV injection is given slowly together with prothrombin complex concentrate (PCC). If PCC is not available, fresh frozen plasma (FFP) may be used. Repeat the dose after 3 hours if no adequate INR response. Not more than 40 mg should be given intravenously in 24 hours. **Less severe hemorrhage** **IV, IM:** 0.5-1 mg doses may be used in asymptomatic elevated INR. Clinical factors should be taken in considerations. **Hypoprothrombinemia Due to Other Causes.** **Oral:** 2.5 to 25 mg or more (rarely up to 50 mg) is recommended. Avoid the oral route if there is a clinical disorder preventing proper absorption.

IV, IM: 2.5 mg to 10 mg or more. Up to 25 mg to 50 mg may be administered as a single dose. Evaluate INR after 6-8 hours, and repeat dose if INR remains prolonged. Modify subsequent dosage based on the INR or clinical condition.

Reversal of anticoagulation prior to surgery

IV: 5 mg for patients requiring emergency surgery that can be delayed for 6-12 hours. If surgery cannot be delayed, give PCC in addition to Phytomenadione and check the INR before surgery.

Elderly: Use a dose that is at the lower end of the ranges.

Dosing: Pediatric

Children with major and life-threatening bleeding.

IV: 5 mg (together with PCC if appropriate, or FFP if PCC is not available).

Children with asymptomatic high INR (>8) with or without mild hemorrhage

IV: 30 micrograms/kg.

Measure the INR after 2 to 6 hours. In case of inadequate response, the dose may be repeated.

Therapy of early and/or late vitamin K deficiency bleeding (VKDB)

IV: Initially 1 mg and further doses as required, depending on clinical picture and coagulation status.

Prophylaxis of vitamin K deficiency bleeding (VKDB)

Healthy neonates of 36 weeks gestation and older

IM: 1 mg administered at birth or soon after birth.

Oral: 2 mg at birth or soon after birth. Thereafter, oral doses of 2 mg are given at 4-7 days of age and at 1 month of age.

Preterm neonates of less than 36 weeks gestation weighing 2.5 kg or greater, and term neonates at special risk (e.g., prematurity, birth asphyxia, obstructive jaundice, inability to swallow, maternal use of anticoagulants or antiepileptics):

IM, IV: 1 mg at birth or soon after birth. The amount and frequency of further doses depend on coagulation status.

Preterm neonates of less than 36 weeks gestation weighing less than 2.5 kg:

IM, IV: 0.4 mg/kg at birth or soon after birth. ≥ 2.5 kg: 1 mg

This parenteral dose should not be exceeded. The amount and frequency of further doses depend on coagulation status.

Antidote therapy to anticoagulant drugs of the coumarin type

Note: inadequate dosing studies in infants and children at this indication.

	For patients continuing to receive a* coumarin *(Partial reversal of anticoagulation) **IV:** The suggested dose is 30 micrograms/kg. ***For patients requiring a complete reversal of a* coumarin *overdose*** **IV:** The suggested dose is 250-300 micrograms/kg. The earliest effect seen with vitamin K treatment is at 4 to 6 hours and therefore, in case of severe hemorrhage, replacement with coagulation factor concentrates may be indicated (discuss with hematologist). Prothrombin time should be measured after 2 to 6 hours. In case of inadequate response, repeat the dose. Frequent monitoring of vitamin K dependent clotting factors is essential in these patients.
Dosage Adjustment	**Renal Impairment: Adult/Pediatric** There are no dosage adjustments. **Hepatic Impairment: Adult/Pediatric** There are no dosage adjustments.
Contra-Indications	Hypersensitivity to Phytomenadione or any component of the formulation.
Adverse Drug Reactions	**Frequency not defined** • **Cardiovascular:** Chest pain, flushing, hypotension, tachycardia, weak pulse • **Central nervous system:** Dizziness • **Dermatologic:** Diaphoresis, eczematous rash, erythema, erythematous rash, pruritic plaques of the skin, urticaria • **Gastrointestinal:** Dysgeusia • **Hepatic:** Hyperbilirubinemia • **Hypersensitivity:** Anaphylactoid reaction, anaphylaxis, hypersensitivity reaction • **Local:** Injection site reaction (including pain, swelling, tenderness) • **Respiratory:** Cyanosis, dyspnea • **Miscellaneous:** Lesion (scleroderma-like)
Monitoring Parameters	• INR/ Prothrombin time should be monitored regularly, and as clinical conditions indicate. • Assess the degree of bleeding. • Assess patient closely for severe hypersensitivity reactions if administering IV.
Drug Interactions	**Orlistat** (may decrease absorption of fat-soluble vitamins): Separate oral phytonadione with 2 hours interval. **Coumarin anticoagulants.** (e.g. warfarin): Phytonadione may diminish temporarily thier anticoagulant effect. Monitor therapy
Pregnancy and Lactation	**Pregnancy:** There is no specific evidence regarding the safety of Phytomenadione in pregnancy. Administer only if the benefits outweigh the risks. **Lactation:** Phytomenadione is present in breast milk. Consider potenitial advers effects versus benefits.

Administration	**Administration: IM** Administer undiluted. **Administration: IV** • When IV administration is unavoidable, inject the drug very slowly. Do not exceed 1 mg/minute. • Can be added to lower end infusions of 0.9% Sodium Chloride or 5% Dextrose. Do not use if the solution is turbid. • Avoid use of other diluents that may contain benzyl alcohol. • When diluted, start administration immediately after dilution. Discard unused portions of diluted solution as well as unused contents of the ampule. **Administration: Oral** • Certain parenteral formulation may be used for oral doses in pediatrics or situations in which tablets cannot be swallowed. • The contents of certain soft gelatin capsules can be administered by cutting the narrow tubular tip off the capsule and squeezing the liquid into the baby's mouth. N.B. Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	• **Fatal hypersensitivity reactions**, including anaphylaxis, may occur during and immediately after IV or IM administration. Reactions have occurred despite dilution to avoid rapid infusion and upon first and subsequent doses. • **Cutaneous Reactions** may occur with the parenteral administration. These reactions include eczematous reactions, scleroderma-like patches, urticaria, and delayed type hypersensitivity reactions. Time of onset ranged from 1 day to a year after parenteral administration. If a reaction occurs, discontinue Phytomenadione and institute medical management. • **Temporary resistance** to prothrombin-depressing anticoagulants may occur especially with larger doses of Phytomenadione. After using a relatively large dose, it may be necessary to use higher doses of anticoagulant, or to use one which acts on a different principle, such as Heparin sodium. Phytomenadione will not counteract the anticoagulant action of heparin. • A failure to respond (shortening of the INR in 2 to 4 hours) may indicate another diagnosis or coagulation disorder. • **Benzyl Alcohol Preservative** Serious and fatal adverse reactions such as “gasping syndrome” can occur in neonates and infants treated with drugs containing benzyl alcohol preservatives. Use preservative-free formulations for neonates and infants.
Storage	Store between 15°C to 30°C; protect from light. Do not use if the solution is turbid. N.B. Refer to manufacturer PIL if there are specific considerations.

Tranexamic acid

Generic Name	Tranexamic acid
Dosage Form/Strengths	**Injection**: 100 mg/ml, 500 mg/5 ml **Tablet**: 500 mg, 650 mg
Route of Administration	IV, Oral
Pharmacologic Category	Antifibrinolytic Agent; Antihemophilic Agent; Hemostatic Agent; Lysine Analog **ATC**: B02AA02
Indications	Tranexamic acid is indicated in adults and children from one year in prevention and treatment of haemorrhages (short term) due to general or local fibrinolysis.
Dosage Regimen	**Dosing: adult** **General fibrinolysis (Standard dose)** **IV:** 15 mg/kg or 1 g three to four times daily by slow IV injection or infusion (1ml/min.). **Local fibrinolysis (Standard dose)** **Oral:** 1 – 1.5 g (15-25 mg /kg) two to three times daily. **IV:** 0.5 – 1 g two to three times daily by slow IV injection or infusion (1ml/min.). **Specific cases** **Prostatectomy (Prophylaxis and treatment of hemorrhage in high-risk patients)** **IV:** commence injection pre- or post-operatively; **then Oral:** 1 g three to four times daily until macroscopic hematuria is no longer present. **Menorrhagia** **Oral:** (For 500 mg tablet) 1 g three times daily if needed for up to 4 days. If very heavy menstrual bleeding, dosage may be increased. Do not exceed a total dose of 4 g daily (8 tablets). Do not initiate treatment until menstrual bleeding has started. (For 650 mg tablet) 1.3 g taken three times daily (3900 mg/day) for a maximum of 5 days during monthly menstruation. **Epistaxis** **Oral:** 1 g three times daily, where recurrent bleeding is anticipated oral therapy should be administered for 7 days. **Conization of the cervix** **Oral:** 1.5 g three times daily. **Traumatic hyphema**

	Oral: 1–1.5 g three times daily. The dose is based on 25 mg /kg bodyweight. **Hereditary angioneurotic edema** **Oral:** 1–1.5 g two to three times daily. In some patients this dosing should be continuous, but intermittent treatment can be used where patients are aware of the onset of the illness. **Haemophilia In the management of dental extractions** **Oral:** 1–1.5 g three time daily. The dose is based on 25 mg /kg bodyweight. **IV:** 10 mg/kg actual body weight administered as a single dose, immediately before tooth extractions, infuse no more than 1 mL/minute. May be administered for 2 to 8 days at a dose of 10 mg/kg 3 to 4 times daily. **Dosing: pediatric** **For the approved indications above** **Children from 1 year:** **Oral**: 25 mg/kg per dose. **IV**: 20mg/kg/day. However, data about safety and efficacy are limited.
Dosage Adjustment	**Renal Impairment: Adult/Pediatric** **IV:** **Serum creatinine <1.4 mg/dL:** No dosage adjustment necessary. **Serum creatinine ≥1.4 to <2.8 mg/dL:** 10 mg/kg every 12 hours. **Serum creatinine ≥2.8 to <5.7 mg/dL:** 10 mg/kg every 24 hours. **Serum creatinine ≥5.7 mg/dL:** 5 mg/kg every 24 hours **OR** 10 mg/kg every 48 hours. **Oral:** **Serum creatinine <1.4 mg/dL:** No dosage adjustment necessary. **Serum creatinine ≥1.4 to <2.8 mg/dL:** 15 mg/kg (or 1300mg) every 12 hours. **Serum creatinine ≥2.8 to <5.7 mg/dL:** 15 mg/kg (or 1300mg) every 24 hours. **Serum creatinine ≥5.7 mg/dL:** 650 mg once a day **Hepatic Impairment: Adult/Pediatric** There are no dosage adjustments.
Contra-Indications	• Hypersensitivity to the active substance or any of the excipients. • Severe renal failure because of risk of accumulation. • Active thromboembolic disease. • History of venous or arterial thrombosis. • Fibrinolytic conditions following consumption coagulopathy. • History of convulsions.

Adverse Drug Reactions	**>10%** • **Gastrointestinal:** Abdominal pain (20%). • **Nervous system:** Headache (50%). • **Neuromuscular & skeletal:** Back pain (21%), musculoskeletal pain (11%). • **Respiratory:** Nasal signs and symptoms (25% including sinus symptoms). **1% to 10%** • **Hematologic and oncologic: Anemia (6%).** • **Nervous system: Fatigue (5%).** • **Neuromuscular and skeletal:** Arthralgia (7%), muscle cramps (≤7%), muscle spasm (≤7%).
Monitoring Parameters	• Ophthalmic examination (visual acuity, optical coherence tomography) regularly if on long-term treatment (>3 months) • Renal function tests. • Signs/symptoms of hypersensitivity reactions. • Seizures (EEG monitoring for patients with history of seizures or who experience myoclonic movements, twitching, or evidence of focal seizures)
Drug Interactions	***Risk X: Avoid combination*** Anti-inhibitor Coagulant Complex (Human), Estrogen Derivatives, Factor IX Complex (Human), Hormonal Contraceptives, Prothrombin Complex Concentrate (Human), Thrombolytic Agents. ***Risk D: Consider therapy modification*** Tretinoin (Systemic).
Pregnancy and Lactation	**Pregnancy** ▪ Limited data. Although studies in animals do not indicate teratogenic effects, as precaution for use, tranexamic acid is not recommended during the first trimester of pregnancy. Consider risk/benefit. **Lactation** ▪ Not recommended due to presence of tranexamic acid in breast milk. Consider risk/benefit.
Administration	**Administration: IV** ▪ Should be administered slowly at a maximum rate (1 ml/min); faster rates may result in hypotension. ▪ For IV infusions: dilute in 50 to 250 mL of NS or D5W. Tranexamic acid may be mixed with most solutions for infusion such as electrolyte solutions, carbohydrate solutions, amino acid solutions, and dextran solutions. Heparin may be added to Injection. Do not mix with blood. It should NOT be mixed with solutions containing penicillin. **Administration: Oral** ▪ Administer without regard to meals. Swallow tablet whole; do not break, chew, or crush. N.B. Refer to manufacturer PIL if there are specific considerations.

Warnings/ Precautions	▪ **Thromboembolic risk:** Avoid the concomitant use with pro-thrombotic medical products, as the risk of thrombosis may be increased. These medications include but are not limited to, Factor IX complex concentrates, Anti-inhibitor coagulant concentrates, and hormonal contraceptives. ▪ **Seizures:** may cause seizures, including focal and generalized seizures. It most commonly occurs following IV injection of tranexamic acid in higher doses than that recommended. Consider dose reduction during surgery and renal dysfunction. ▪ **Hypersensitivity reactions:** including anaphylactic reactions have occurred with the IV use. If serious reaction happens, discontinue treatment, provide appropriate medical management, and do not reinitiate treatment. ▪ **Visual disturbances:** Retinal degeneration have occurred in animals after oral or IV administration at long period of time. Patients expected to be treated for greater than 3 months may consider ophthalmic monitoring. ▪ **Dizziness**: May cause dizziness and will be worsened if used concomitantly with other dizziness-causing drugs. Patients should avoid driving or using machines until they know how Tranexamic acid affects them. ▪ **Use in Hematuria:** Close monitoring is recommended for patients with haematuria or risk of haematuria from the upper urinary tract due to risk for urinary obstruction. ▪ **Disseminated intravascular coagulation (DIC)**: Tranexamic acid should not be used in most cases. If Tranexamic acid is given it must be restricted to those in whom there is predominant activation of the fibrinolytic system with acute severe bleeding. In such acute case, a single dose of 1g Tranexamic acid is usually sufficient to control bleeding. Do not use unless appropriate haematological laboratory facilities and expertise are available. ▪ **Subarachnoid Hemorrhage:** Using Tranexamic acid in women with subarachnoid hemorrhage may result in cerebral edema and cerebral infarction. Use is not recommended for these patients.
Storage	**Injection**: Store between 15°C to 30°C. **Tablets**: Store between 15°C to 30°C. N.B. Refer to manufacturer PIL if there are specific considerations**.**

Antiplatelet Agents

Acetylsalicylic Acid Refer to Cardiovascular Formulary

Cilostazol Refer to Cardiovascular Formulary

Clopidogrel Refer to Cardiovascular Formulary

Ticagrelor Refer to Cardiovascular Formulary

Tirofiban

Generic Name	Tirofiban
Dosage Form/Strengths	**Concentrate for Solution for I.V Infusion**: 12.5 mg/50 ml (0.25/ml), 12.5 mg/250 ml (0.05/ml).
Route of Administration	IV
Pharmacologic Category	Antiplatelet Agent, Glycoprotein IIb/IIIa Inhibitor ATC: B01AC17
Indications	• Reduce the rate of thrombotic cardiovascular events (combined endpoint of death, myocardial infarction, refractory ischemia/repeat cardiac procedure) in adult patients with non-ST elevation acute coronary syndrome (NSTEACS). N.B. Tirofiban should be administered with unfractionated heparin and oral antiplatelet therapy, including acetylsalicylic acid (ASA).
Dosage Regimen	**Adult dosing** • NSTE-ACS patients planned to undergo PCI within the first 4 hours of diagnosis or in patients with acute myocardial infarction intended for primary PCI **Initial: IV bolus**: 25 mcg/kg given over 3 – 5 minutes, followed by a continuous infusion at a rate of 0.15 mcg/kg/min for 12-24, and up to 48 hours. • Early invasive strategy for NSTE-ACS (but not planned to undergo angiography for at least 4 hours and up to 48 hours after diagnosis. **Initial**: **IV infusion**: 0.4 mcg/kg/min for 30 minutes. **Maintenance** infusion rate of 0.1 mcg/kg/min for at least 48 hours. Infusion of tirofiban and unfractionated heparin may be continued during coronary angiography and should be maintained for at least 12 hours and up to 24 hours after angioplasty/atherectomy. . **Pediatrics** The safety and efficacy in children aged <18 years have not been established.
Dosage Adjustment	**Renal Impaiment** • CrCl 30-60 ml/min: Carefully monitor for bleeding. • Severe renal failure (CrCl <30 ml/min): Dosage is reduced to 50%. **Hepatic Impaiment** • Mild to moderate liver insufficiency: Caution. • Severe hepatic impairment: No data. Use is not recommended.
Contra-Indications	• Hypersensitivity to tirofiban or any of the excepients. • Active or recent internal bleeding, major surgical procedure or severe physical trauma within the previous month. • Known history of intracranial disease (e.g. neoplasm, arteriovenous malformation, aneurysm).

	• Thrombocytopenia (platelet count <100,000/mm^3) or clotting disturbances (e.g. prothrombin time > 1.3 times normal or INR >1.5). • Malignant hypertension. • Severe liver failure.
Adverse Drug Reactions	**1% to 10%** **Cardiovascular**: Bradycardia (4%), coronary artery dissection (5%), edema (≤2%), vasodepressor syncope (2%). **Dermatologic**: Diaphoresis (2%). **Genitourinary**: Pelvic pain (6%). **Hematologic & oncologic**: Thrombocytopenia (≤2%). **Nervous system:** Dizziness (3%). **Neuromuscular & skeletal**: Lower extremity pain (3%). **Miscellaneous**: Swelling (≤2%).
Monitoring Parameters	• CBC prior to therapy and within 2-6 hours after start of therapy with tirofiban and at least once daily thereafter while on therapy. • Activated thromboplastin time (APTT) prior to therapy and repeatedly to adjust dose. • Renal and hepatic functions.
Drug Interactions	***Risk X: Avoid combination*** Abrocitinib ***Risk D: Consider therapy modification*** Caplacizumab Fondaparinux
Pregnancy and Lactation	**Pregnancy**: Limited data. Published data cannot definitively establish the association or absence of risk. Consider benefit and risk. **Lactation**: Limited data. Not recommended during breastfeeding due to potential fetal risk.
Administration	**Intravenous administration:** **IV infusion:** Dilution with saline or dextrose 5% is needed before use. May be administered with heparin though the same infusion tube. N.B. Refer to manufacturer PIL if there are specific considerations.
Warnings/ Precautions	**Concomitant therapy**: The safety and efficacy of tirofiban with low molecular weight heparins or thrombolytic therapy have not been investigated. **Bleeding**: Use is not recommended in cases where an increased risk of bleeding is suspected. In cases of major or uncontrollable bleeding, tirofiban should be discontinued immediately. **Thrombocytopenia:** Profound thrombocytopenia has been reported. Monitoring platelet counts is necessary. If the platelet count decreases to < 90,000/mm^3, further platelet counts should be carried out to exclude pseudothrombocytopenia. If thrombocytopenia is confirmed, tirofiban, and heparin, should be discontinued. Previous exposure to a glycoprotein

	(GP) IIb/IIIa receptor antagonist may increase the risk of developing thrombocytopenia. **Elderly, female patients, and patients with low body weight** have a higher incidence of bleeding complications. Caution.
Storage	Store between 15–30 °C. Do not freeze. Protect from light Use immediately after opening. N.B. Refer to manufacturer PIL if there are specific considerations.

Iron Chelator

Deferasirox

Generic Name	Deferasirox
Dosage Form/Strengths	Fil coated tablet: 90mg, 180mg, 360mg. Dispersible tablets for oral suspension: 125mg, 250mg, 500mg.
Route of Administration	Oral
Pharmacologic Category	**Chelating agent.** **ATC:** V03AC03
Indications	• Treatment of chronic iron overload due to blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients 2 years of age and older. • Treatment of chronic iron overload non-transfusion-dependent - thalassemia syndromes when deferoxamine therapy is contraindicated in patients aged 10 years and older with a liver iron (Fe) concentration (LIC) of at least 5 mg Fe per gram of dry weight (Fe/g dw) and a serum ferritin greater than 300 mcg/L.
Dosage Regimen	**Adults and pediatrics dosing** **Film coated tablets** **Transfusional iron overload** **Initial**: 14 mg/kg starting after taking 20 units (about 100 ml/kg of packed red blood cells) or when serum ferritin >1,000 µg/l. **Or** initial daily dose of 21 mg/kg may be considered if receiving more than 14 ml/kg/month of packed red blood cells (approximately >4 units/month for an adult). **Or** 7 mg/kg daily may be considered for patients who do not require reduction of body iron levels and who are also receiving less than 7 ml/kg/month of packed red blood cells (approximately <2 units/month for an adult). **Or** one third dose of the deferoxamine If patient is well managed on deferoxamine. **Adjust dose** every 3-6 months (every month for pediatric) based on ferritin level. Dose adjustments may be made in steps of 3.5 to 7 mg/kg (increase dose if > 2,500 µg/l ferritin or decrease if ≤2,500 µg/l). Treatment should be **discontinued** if serum ferritin falls consistently below 500 µg/l. **Non-transfusion-dependent thalassemia syndromes** **Initial**: 7 mg/kg when liver iron concentration (LIC) ≥5 mg Fe/g dw or Serum ferritin >800 µg/l. **Adjust dose** every 3-6 months (every month for pediatric). Dose adjustments may be made in steps of 3.5 to 7 mg/kg (increase dose if liver iron concentration ≥7 mg Fe/g dw or Serum ferritin >2000 µg/l or decrease if liver iron concentration <7 mg Fe/g dw or Serum ferritin ≤2000 µg/l). **Maximum dose** 14 mg/kg/day for adult patients, 7 mg/kg/day for pediatric patients.

Treatment should be **discontinued** if liver iron concentration <3 mg Fe/g dw or Serum ferritin ≤300 µg/l.
N.B. LIC is the preferred method of iron overload determination.

N.B. Larger dose of the dispersible tablets is needed in comparison to the recommended dose for the film-coated tablets due to difference in bioavailability.

	Film coated tablet	**Tablets for oral suspension**
Transfusion-Dependent Iron Overload		
Starting Dose	14 mg/kg/day	20 mg/kg/day
Titration Increments	3.5-7 mg/kg	5-10 mg/kg
Maximum Dose	28 mg/kg/day	40 mg/kg/day
If well managed on deferoxamine	One third dose of deferoxamine	Half dose of deferoxamine.
Non-Transfusion-Dependent Thalassemia Syndromes		
Starting Dose	7 mg/kg/day	10 mg/kg/day
Titration Increments	3.5-7 mg/kg	5-10 mg/kg
Maximum Dose	14 mg/kg/day	20 mg/kg/day

Dosage Adjustment

Renal Impairment

- CrCl < 60 ml/min: Contraindicated.
- During therapy: If CrCl < 90 ml/min and serum creatinine >33% above pretreatment average at two consecutive visits: Reduction of daily dose by 7 mg/kg/day is required. Interrupt after dose reduction if remined CrCl < 90 ml/min or serum creatinine >33% above pretreatment average

Hepatic Impairment

- Moderate hepatic impairment (Child Pugh Class B): Decrease dose. Not to exceed 50% of normal dose.
- Severe hepatic impairment (Child-Pugh Class C)

Contra-Indications

- Hypersensitivity to the active substance or to any of the excipients.
- Combination with other iron chelator. Not studied.
- Patients with estimated creatinine clearance <60 ml/min.

Adverse Drug Reactions

>10%

Dermatologic: Skin rash (6% to 11%).
Gastrointestinal: Abdominal pain (21% to 28%), diarrhea (5% to 20%), nausea (6% to 23%), vomiting (10% to 21%).
Genitourinary: Proteinuria (19%).
Renal: Increased serum creatinine (7% to 11%; increase >33% from baseline at 2 consecutive visits: 3% to 38%).

1% to 10%

Cardiovascular: Edema.
Dermatologic: Dyschromia.
Endocrine & **metabolic**: Fanconi's syndrome.
Gastrointestinal: Acute pancreatitis, cholelithiasis, duodenal ulcer, gastric ulcer, gastritis, gastrointestinal hemorrhage.

	Hepatic: Increased serum alanine aminotransferase (>5 x ULN: 1% to 8%) **Nervous system**: Anxiety, dizziness, fatigue, sleep disorder. **Ophthalmic**: Cataract, maculopathy. **Otic**: Hearing loss (including high frequency). **Renal**: Renal tubular disease. **Respiratory**: Pharyngolaryngeal pain. **Miscellaneous**: Fever.
Monitoring Parameters	• Serum ferritin be monitored every month. • Monitor LIC every 6 months in non-Transfusion-Dependent Thalassemia Syndromes. • Hepatic prior to therapy and every 2 weeks during the first month and then every month. • Kidney functions (serum creatinine and creatinine clearance) monitored prior to therapy (in duplicate), weekly in the first month after starting or modifying dose (including switch of formulation), and monthly thereafter. • Proteinuria: Prior to therapy and monthly thereafter. • Auditory and ophthalmic: testing Prior to therapy and annually thereafter. • Body weight, height and sexual development: Prior to therapy and annually in pediatric patients. • CBC monthly during therapy.
Drug Interactions	***Risk X: Avoid combination*** Aluminum Hydroxide, Amodiaquine, Fezolinetant, Tovorafenib. ***Risk D: Consider therapy modification*** Alosetron, Belumosudil, Bendamustine, Bile Acid Sequestrants, Busulfan, Daprodustat, Pirfenidone, Rasagiline, Resmetirom, Selexipag, Theophylline Derivatives, Tizanidine, UGT1A1 Inducers.
Pregnancy and Lactation	**Pregnancy** No data. Potential toxicity. Use is not recommended unless clearly necessary. Deferasirox may decrease the efficacy of hormonal contraceptives. Women of childbearing potential are recommended to use additional or alternative non-hormonal methods of contraception when using deferasirox. **Lactation** No data. Not recommended.
Administration	**Oral administration** • Tablet is taken whole with water on an empty stomach or with a light meal. Tablets may be crushed and administered by sprinkling the full dose onto soft food and taken immediately. • The dispersible tablets are dispersed by stirring in a glass of water or orange or apple juice (100 to 200 ml) until a fine dispersion is obtained and taken immediately on an empty stomach. Taken preferably at the same time each day. N.B. Refer to manufacturer PIL if there are specific considerations.

Warnings/ Precautions	**Acute Kidney Injury:** May cause serious and fatal acute kidney injury, including acute renal failure requiring dialysis and renal tubular toxicity including Fanconi syndrome. Patients with pre-existing renal conditions and patients who are receiving medications that depress renal function may be at higher risk of complications. Measure serum creatinine in duplicate before starting therapy. Monitor renal function during therapy and reduce dose or interrupt therapy for toxicity. **Hepatic Toxicity**: Deferasirox may cause serious and fatal hepatic toxicity. Monitor hepatic function. Reduce dose or interrupt therapy for toxicity. **Fatal and Nonfatal Gastrointestinal (GI) toxicities**: Bleeding, ulceration, and irritation may occur. Risk may be greater in patients who are taking deferasirox in combination with drugs that have known ulcerogenic or hemorrhagic potential. **Bone Marrow Suppression**: Neutropenia, agranulocytosis, worsening anemia, and thrombocytopenia, including fatal events; monitor blood counts during therapy. Interrupt therapy for toxicity. **Elderly and pediatrics**: Monitor closely for toxicity. **Hyperammonemia**: Ammonia levels should be measured considering hyperammonemia encephalopathy in patients who develop unexplained changes in mental status while on deferasirox therapy. **Hypersensitivity Reactions**: such as anaphylaxis and angioedema) have been reported. Onset mostly occur within the first month of treatment. Discontinue for severe reactions and institute medical intervention. **Severe Skin Reactions** including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) may occur. Discontinue for severe reactions and should not be reintroduced. **Dehydration**: Care should be taken to maintain adequate hydration in patients who experience volume-depleting events (such as diarrhea or vomiting), particularly in children with acute illness. **Vision and hearing**: Monitor disturbances. If disturbances are noted during the treatment, dose reduction or interruption may be considered.
Storage	**S**tore between 15-30 ^{o}C. Keep the bottle closed tightly and away from moisture. N.B. Refer to manufacturer PIL if there are specific considerations.

Erythropoiesis-Stimulating Agent

Erythropoietin Refer to Conventional Anticancer Formulary

Fibrinolytics Agents

Alteplase Refer to Cardiovascular Formulary

Streptokinase Refer to Cardiovascular Formulary

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/

Alphabetical List of content