Refusal Public Assessment report for The Human Medicinal Product

(Diclofenac Potassium 15 mg/ml Oral Drops)

**Overview

Based on the review of safety & efficacy data, The Egyptian Drug Authority (EDA) refused granting the marketing authorization for a medicinal product containing the following formula:
Diclofenac Potassium 15 mg/ 1 ml as oral drops

**Legal basis for application

The application is submitted to Scientific Evaluation unit for pharmaceutical products and Drug Development according to Ministerial decree decision 150/2022

**Applied Scientific Information

- Pharmacotherapeutic group

Diclofenac Potassium: Non-steroidal anti-inflammatory drugs (NSAID)

- Therapeutic indication

Applied Indication:

Short-term treatment in the following acute conditions: post-traumatic and post-operative pain, inflammation and swelling, e.g., following dental or orthopedic surgery. As an adjuvant in severe painful inflammatory infections of the ear, nose or throat, e.g., pharyngotonsillitis, otitis. In keeping with general therapeutic principles, the underlying disease should be treated with basic therapy, as appropriate. Fever alone is not an indication.

- Therapeutic dose:

Applied Dose:

Children aged 1 year or over and adolescents should be given 0.5 mg to 2 mg/kg body weight (1 to 4 drops) daily, depending on the severity of the disorder. For adolescents aged 14 or over, 75 to 100 mg daily is usually sufficient. The total daily dose should generally be divided in 2 to 3 doses. The maximum daily dose of 150 mg should not be exceeded.

- Warnings associated with the drug:

Applied Warnings:

- Gastrointestinal bleeding, ulceration or perforation.

- Serious skin reactions, some of them fatal, including exfoliative dermatitis, Steven-Johnson syndrome and toxic epidermal necrolysis.

-Cardiovascular Risk

The use of NSAIDs particularly at high doses and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

-Pre-existing asthma

In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary disease or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions on NSAIDs like asthma exacerbations (so called intolerance to analgesics/analgesics-asthma), Quincke's oedema or urticaria are more frequent than in other patients.

**Scientific Assessment

*** By Searching in Reference countries, it was found that:**

- Diclofenac Potassium as Oral Drops is not available in any Reference countries.
- Diclofenac Sodium as Oral Drops is valid in Swiss medic till 18/12/2023.

Trade name	Generic name	Dosage form	Registration holder
Voltaren, drops	Diclofenacum resinate 43.7 mg eq. To Diclofenac sodium 15 mg/1ml	drops - 20 ml	Novartis Pharma Schweiz AG

Indication:
Voltaren oral drops are suitable for the treatment of diseases that are accompanied by inflammation, painful inflammation after accidental injuries, inflammation & pain after dental & surgical procedure, rheumatic diseases in childhood & as a complementary treatment for various painful, acute infectious diseases especially in the area of the ears, nose & throat.

Dose:
Voltaren drops for oral use are particularly suitable for use in children, as they allow an individual dosage adapted to the child's body weight according to the specified dosage range (1 drop = 0.5 mg).
Depending on the severity of the disease, children from 1 year and adolescents receive 0.5-2 mg per kg of body weight daily, divided into 2-3 individual doses. For the treatment of juvenile chronic polyarthritis, the daily dose can be divided into several individual doses and increased to a maximum of 3 mg per kg of body weight.
The maximum daily dose of 150 mg should not be exceeded.
The drop bottle containing the suspension should be shaken well before administration.
Voltaren should not be used in children under the age of 1 year.

***Diclofenac potassium as oral solution ia available in FDA online as follow:**

Trade name	Generic name	Dosage form	Company	Status
Cambia	Diclofenac potassium 50mg	For solution; oral	ASSERTIO	Prescription **Initial U.S. Approval:** 1988

Indication:
Acute treatment of migraine attacks with or without aura in adults 18 years of age or older

Dose:
Single 50 mg dose; mix single packet contents with 1 to 2 ounces (30 to 60 mL) of water prior to administration

***according to BNF for children 2020-2021:**

Available dosage forms: tablet

Indications And dose of diclofenac potassium According to BNF Children 2020-2021:
Pain and inflammation in rheumatic disease and other musculoskeletal disorders.

▶ Child 14–17 years: 75–100 mg daily in 2–3 divided doses.
Postoperative pain
▶ Child 9–13 years (body-weight 35 kg and above): Up to 2 mg/kg daily in 3 divided doses; maximum 100 mg per day.
▶ Child 14–17 years: 75–100 mg daily in 2–3 divided doses
Fever in ear, nose, or throat infection.
▶ Child 9–17 years (body-weight 35 kg and above): Up to 2 mg/kg daily in 3 divided doses; maximum 100 mg per day.

According to Lexicomb:

Mechanism of action.

Reversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which results in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties.
Other proposed mechanisms not fully elucidated (and possibly contributing to the anti-inflammatory effect to varying degrees), include inhibiting chemotaxis, altering lymphocyte activity, inhibiting neutrophil aggregation/activation, and decreasing proinflammatory cytokine levels.

Dosing: Pediatric

Oral:
Acute pain (mild to moderate): Children ≥12 years and Adolescents: Oral: 25 mg 4 times daily.
Juvenile idiopathic arthritis: Limited data available: Children and Adolescents: Oral: 2 to 3 mg/kg/day in divided doses 2 to 3 times daily; maximum daily dose: 150 mg/day.
Migraine: Limited data available: Children ≥12 years and Adolescents: Oral: 50 mg as a single dose at onset of migraine.

Warnings and precautions:

Concerns related to adverse effects:

- Anaphylactoid reactions: Even in patients without prior exposure anaphylactoid reactions may occur; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Contraindicated in patients who experience bronchospasm, asthma, rhinitis, or urticaria with nonsteroidal anti-inflammatory drug (NSAID) or aspirin therapy.
- Cardiovascular events: NSAIDs cause an increased risk of serious (and potentially fatal) adverse cardiovascular thrombotic events, including MI and stroke. Risk may occur early during treatment and may increase with duration of use. Relative risk appears to be similar in those with and without known cardiovascular disease or risk factors for cardiovascular disease; however, absolute incidence of serious cardiovascular thrombotic events (which may occur early during treatment) was higher in patients with known cardiovascular disease or risk factors and in those receiving higher doses. Avoid use in patients with recent MI unless benefits outweigh risk of cardiovascular thrombotic events. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternate therapies should be considered for patients at high risk.

*CNS effects: May cause drowsiness, dizziness, blurred vision, and other neurologic effects which may impair physical or mental abilities; patients must be cautioned about performing tasks which require

mental alertness. Discontinue use with blurred or diminished vision and perform ophthalmologic exam. Periodically evaluate vision in all patients receiving long term therapy.

*Drug reaction with eosinophilia and systemic symptoms: Potentially serious, sometimes fatal, drug reaction with eosinophilia and systemic symptoms (DRESS), also known as multiorgan hypersensitivity reactions, has been reported with NSAIDs. Monitor for signs and symptoms (eg, fever, rash, lymphadenopathy, eosinophilia) in association with other organ system involvement (eg, hepatitis, nephritis, hematological abnormalities, myocarditis, myositis). Early symptoms of hypersensitivity reaction (eg, lymphadenopathy, fever) may occur without rash.

*GI events: NSAIDs cause an increased risk of serious GI inflammation, ulceration, bleeding, and perforation (may be fata); elderly patients and patients with history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events. These events may occur at any time during therapy and without warning.

*Hematologic effects: Platelet adhesion and aggregation may be decreased; may prolong bleeding time; patients with coagulation disorders or who are receiving anticoagulants should be monitored closely. Anemia may occur; patients on long-term NSAID therapy should be monitored for anemia. Rarely, NSAID use has been associated with potentially severe blood dyscrasias (eg, agranulocytosis, thrombocytopenia, aplastic anemia**).**

*Hepatic effects: Transaminase elevations have been reported with use; closely monitor patients with any abnormal LFT. Rare, sometimes fatal severe hepatic reactions (eg, fulminant hepatitis, hepatic necrosis, hepatic failure) have occurred with NSAID use; discontinue immediately if clinical signs or symptoms of liver disease develop or if systemic manifestations occur.

*Renal effects: NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation (usually reversible). Patients with impaired renal function, dehydration, hypovolemia, heart failure, hepatic impairment, those taking diuretics and ACE inhibitors, and elderly patients are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Long-term NSAID use may result in renal papillary necrosis and other renal injury.

*Skin reactions/hypersensitivity: NSAIDs may cause potentially fatal serious skin adverse events, including drug reaction with eosinophilia and systemic symptoms, exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); may occur without warning; discontinue use at first sign of skin rash (or any other hypersensitivity).

Adverse Reactions:

The following adverse drug reactions and incidences are derived from product labeling unless otherwise specified. Adverse reactions may be reported for diclofenac specifically or as class effects for nonsteroidal anti-inflammatory drugs.

- **>10%:**

Cardiovascular: Edema (33%)
Gastrointestinal: Nausea (3% to 14%)

- **1% to 10%:**

Cardiovascular: Hypertension (2%)
Dermatologic: Diaphoresis (1%), pruritus (7%), skin rash
Gastrointestinal: Abdominal pain (4% to 7%), constipation (8%), diarrhea (6%), duodenal ulcer, dyspepsia (2%), flatulence (2% to 3%), gastric ulcer, gastrointestinal hemorrhage, gastrointestinal perforation, heartburn, upper abdominal pain (3%), vomiting (3% to 6%)
Hematologic & oncologic: Anemia, prolonged bleeding time
Hepatic: Increased liver enzymes, increased serum alanine aminotransferase (2%), increased serum aspartate aminotransferase
Nervous system: Dizziness (1% to 4%), drowsiness (3%), headache (4% to 10%)
Neuromuscular & skeletal: Back pain (4%), limb pain (3%), musculoskeletal pain (4%)
Otic: Tinnitus
Renal: Increased serum creatinine (2%), renal function abnormality
Respiratory: Sinusitis (3%).

- **<1%:**

Cardiovascular: Acute myocardial infarction, cardiac arrhythmia, cardiac failure, flushing, hypotension, palpitations, syncope, tachycardia, vasculitis
Dermatologic: Alopecia, ecchymoses, erythema multiforme, exfoliative dermatitis, skin photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria
Endocrine & metabolic: Hyperglycemia, weight changes
Gastrointestinal: Change in appetite, colitis, eructation, esophagitis, gastritis, glossitis, hematemesis, melena, pancreatitis, peptic ulcer, stomatitis, xerostomia
Genitourinary: Cystitis, dysuria, hematuria, oliguria, proteinuria
Hematological & oncologic: Agranulocytosis, aplastic anemia, eosinophilia, hemolytic anemia, leukopenia, lymphadenopathy, pancytopenia, purpuric disease, rectal hemorrhage, thrombocytopenia
Hepatic: Fulminant hepatitis, hepatic failure, hepatic necrosis, hepatitis, jaundice
Hypersensitivity: Anaphylaxis, angioedema
Infection: Infection, sepsis
Nervous system: Abnormal dreams, anxiety, coma, confusion, depression, hallucination, insomnia, malaise, meningitis, nervousness, paresthesia, seizure, vertigo
Neuromuscular: Asthenia, tremor
Ophthalmic: Blurred vision, conjunctivitis
Otic: Auditory impairment
Renal: Interstitial nephritis, polyuria, renal failure syndrome
Respiratory: Asthma, dyspnea, pneumonia, respiratory depression
Miscellaneous: Fever

****According to Martindale:**
Administration :

In children 1 to 12 years old the licensed UK oral or rectal dose of diclofenac sodium for juvenile idiopathic arthritis is 1 to 3 mg/kg daily in divided doses. In children 6 to 12 years old diclofenac sodium may also be given rectally for the treatment of acute postoperative pain, either alone or as an adjunct to opiate therapy; a usual dose is 1 to 2 mg/kg daily in divided doses for a maximum of 4 days. The parenteral route is not licensed for use in children although it has been used

The BNFC suggests slightly different doses of diclofenac sodium: in the management of rheumatic disease, including juvenile idiopathic arthritis, in children from 6 months of age, it recommends an oral dose of 3 to 5 mg/kg daily, in 2 or 3 divided doses, up to a maximum of 150 mg daily. For relief of pain and inflammation in, for example, soft-tissue disorders, the recommended oral or rectal dose in children from 6 months of age is 0.3 to 1 mg/kg given three times daily; children 2 years of age and older may be given a similar dose once or twice daily by intravenous infusion or deep intramuscular (gluteal) injection instead, for up to 2 days. a maximum daily dose of 150 mg should not be exceeded

Diclofenac potassium has also been used in children aged over 14 years for the treatment of rheumatic disease, musculoskeletal disorders, and postoperative pain; it is given in an oral dose of 75 to 100 mg daily in 2 to 3 divided doses**.**

***According to the report of general administration of pharmaceutical vigilance:**

**The active ingredient diclofenac potassium in the form and pharmaceutical concentration (Diclofenac Potassium 15 mg/ml Oral Drops) was not found in any of the reference authorities.

An article entitled **Safety review of diclofenac published on 10/2014 on the website of the Australian Drug Regulatory Authority, It states the safety of diclofenac and is summarized as follows:

Examining the recent literature regarding the safety of diclofenac, cardiovascular safety is the most published topic. The cardiovascular safety of NSAIDs was examined in a TGA review in 2012, however an additional review of the evidence for harm incorporating new evidence is presented below. The GI adverse effects of diclofenac are well known and the recent literature on this is summarized. Hepatic adverse effects are specifically examined. There were no other significant safety issues identified in the review of the recent literature.

**An article is published on 2021 in Embase site with title "An open-label study evaluating the pharmacokinetics and safety of diclofenac potassium for oral solution for the acute treatment of migraine with or without aura in pediatric participants" and is summarized as follows :

Diclofenac potassium for Oral Solution exhibited a favorable pharmacokinetic and safety profile in 12-17 year-old patients with a diagnosis of episodic migraine with/without aura.

**Conclusion

Based on Scientific assessment & applied data for the submitted medicinal product:

The applicant did not submit clinical data or scientific evidence supporting the use of Diclofenac Potassium as Oral drops for infants. Diclofenac Potassium is not available as oral drops in any scientific reference or reference country. According to BNF for Children 2020-2021, diclofenac potassium is used from 9 years old in postoperative pain & fever in ear, nose or throat infection.

The Scientific Evaluation committee adopted a negative opinion, recommending the refusal of the marketing authorization for a medicinal product containing Diclofenac Potassium 15 mg/ml as oral drops based on the following reasons :

1- No sufficient clinical data or scientific evidences supporting the use of diclofenac Potassium as oral drops for infants are submitted.
2- Diclofenac potassium as oral drops may be misused in infants as it is used from 9 years old according to BNF for children 2020-2021

Pharmaceutical Vigilance committee has a concern about registration of the product due to the difficulty of controlling the dosage in the pharmaceutical form Oral drops, which leads to serious problems for infants & based on scientific evaluation committee decision. In addition that this formulation has no any reference.

The Technical committee of drug control refused granting the marketing authorization for a medicinal product containing Diclofenac Potassium 15 mg/ml as oral drops .