

## **Summary of Product Characteristics**

## **1. NAME OF THE MEDICINAL PRODUCT**

REGUNAC (Diclofenac Potassium Tablets USP 50 mg)

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film coated Tablet contains:

Diclofenac Potassium USP 50 mg

For a full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Film Coated Tablet

Dark blue color, circular, slightly biconvex, film coated tablets, plain on both sides.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Treatment of:

- Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, juvenile rheumatoid arthritis (JRA), ankylosing spondylitis, osteoarthritis and spondylarthritis, painful syndromes of the vertebral column, non-articular rheumatism.
- Acute attacks of gout.
- Symptomatic, short-term treatment of post-traumatic and post-operative pain (POP), inflammation and swelling, e.g. following dental or orthopaedic surgery.
- Painful and/or inflammatory conditions in gynaecology, e.g. primary dysmenorrhoea or adnexitis.
- Symptomatic short-term treatment of pain related to inflammatory infections of the ear, nose or throat, e.g. pharyngotonsillitis, otitis (ENT). In keeping with general therapeutic principles, the underlying disease should be treated with anti-infective basic therapy, as therapeutically appropriate. Fever alone without inflammatory component is not an indication.

### **4.2 Posology and method of administration**

As a general recommendation, the dose should be individually adjusted. The tablets should be swallowed whole with liquid, preferably before meals, and must not be divided or chewed.

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4 Special warnings and precautions for use).

General target population:

Adults

The recommended initial daily dose is 100 to 150 mg. In milder cases, as well as for long-term therapy, 75 to 100 mg daily is usually sufficient. The total daily dose should generally be divided into 2 to 3 doses. To suppress nocturnal pain and morning stiffness, treatment with tablets during the day can be supplemented by the administration of a suppository at bedtime (up to a total maximum daily dose of 150 mg).

In primary dysmenorrhoea, the daily dose should be individually adjusted and is generally 50 to 150 mg. A dose of 50 to 100 mg should be given initially and, if necessary, increased

over the course of several menstrual cycles up to a maximum of 200 mg/day. Treatment should be started on appearance of the first symptoms and, depending on the symptomatology, continued for a few days.

Special populations:

Paediatric patients (below 18 years of age)

Children aged 9 years (min. 35 kg BW) or over and adolescents should be given up to 2 mg/kg body weight per day in 3 divided doses, depending on the severity of the disorder. Because of their dosage strength, Diclofenac 50 mg gastro-resistant tablets are not recommended for use in children and adolescents below 14 years of age; Diclofenac 25 mg gastro-resistant tablets could be used in these patients.

Table: Dose recommendations for acute indications POP and ENT

<b>Body weight (kg) (corresponding age)</b>	<b>Dosage forms</b>	<b>Single dose in number of drops, tablets, suppositories (corresponding diclofenac dose)</b>	<b>Maximum daily dose in number of dosage units (drops/tablets/suppositories)</b>
13-19 kg (2 - 5 yr.)	12.5 mg sup	12.5 mg	12.5 mg bid - 12.5 mg tad
20-44 kg (6-11 yr.)	12.5 mg sup	12.5 mg	12.5 mg tid
35-44 kg (9-11 yr.)	25 mg sup/tab	25 mg	25 mg tid
45-55 kg (12-16 yr)	25 mg sup/tab	25 mg	25 mg tid – 25 mg four times daily

#### **Geriatric patients (aged 65 years or above)**

No adjustment of the starting dose is generally required for elderly patients. However, caution is indicated on basic medical grounds, especially for frail elderly patients or those with a low body weight (see section 4.4 Special warnings and precautions for use). Congestive heart failure (NYHA-I) or significant cardiovascular risk factors Patients with congestive heart failure (NYHA-I) or significant risk factors for cardiovascular disease should be treated with Diclofenac only after careful consideration and only at doses ≤100mg daily if treated for more than 4 weeks (see section 4.4 Special warnings and precautions for use)

#### **Renal impairment**

Diclofenac is contraindicated in patients with renal failure (GFR<15mL/min./1.73m<sup>2</sup>) (see section 4.3 Contraindications). No specific studies have been carried out in patients with renal impairment, therefore, no specific dose adjustment recommendations can be made. Caution is advised when administering Diclofenac to patients with renal impairment (see section 4.4 Special warnings and precautions for use).

### **Hepatic impairment**

Diclofenac is contraindicated in patients with hepatic failure (see section 4.3 Contraindications). No specific studies have been carried out in patients with hepatic impairment, therefore, no specific dose adjustment recommendations can be made. Caution is advised when administering Diclofenac to patients with mild to moderate hepatic failure (see section 4.4 Special warnings and precautions for use).

### **Method of administration**

The tablets should be swallowed whole with liquid, preferably before meals, and must not be divided or chewed.

## **4.3 Contraindications**

- Known hypersensitivity to the active substance or to any of the excipients.
- Active gastric or intestinal ulcer, bleeding or perforation (see sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects)
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
- Last trimester of pregnancy (see section 4.6 Fertility, pregnancy and lactation).
- Hepatic failure
- Renal failure (GFR<15mL/min./1.73m<sup>2</sup>)
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), Diclofenac is also contraindicated in patients in whom the use of acetylsalicylic acid or other NSAIDs can precipitate asthma, angioedema, urticaria, or acute rhinitis (i.e. NSAID-induced cross-reactivity reactions) (see section 4.4 Special warnings and precautions for use and 4.8 Undesirable effects). Established congestive heart failure (NYHA II-IV), ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

## **4.4 Special warnings and precautions for use**

### **General**

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below). The concomitant use of Diclofenac with systemic NSAIDs including cyclooxygenase-2 selective inhibitors, should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects.

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases with diclofenac without earlier exposure to the drug. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to diclofenac.

Diclofenac gastro-resistant tablets contain lactose and therefore are not recommended for patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.

## **Gastrointestinal effects**

Gastrointestinal bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs, including diclofenac, and may occur at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events. They generally have more serious consequences in the elderly. If gastrointestinal bleeding or ulceration occurs in patients receiving Diclofenac, the treatment should be discontinued.

NSAIDs, including diclofenac, may be associated with increased risk of gastro-intestinal anastomotic leak. Close medical surveillance and caution are recommended when using diclofenac after gastro-intestinal surgery.

As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be exercised when prescribing Diclofenac in patients with symptoms indicative of gastrointestinal (GI) disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation (see section 4.8 Undesirable effects). The risk of GI bleeding is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation. The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with hemorrhage or perforation, and in the elderly, the treatment should be initiated and maintained at the lowest effective dose.

Combination therapy with protective agents (e.g. proton pump inhibitors or misoprostol) should be considered for these patients, and also for patients requiring concomitant use of low-dose acetylsalicylic acid (ASA)/aspirin or other drugs likely to increase gastrointestinal risk.

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding). Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants, anti-platelet agents or selective serotonin-reuptake inhibitors (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Close medical surveillance and caution should also be exercised in patients with ulcerative colitis or Crohn's disease, as their condition may be exacerbated (see section 4.8 Undesirable effects).

## **Hepatobiliary effects**

Close medical surveillance is required when prescribing Diclofenac to patients with impaired hepatic function, as their condition may be exacerbated.

As with other NSAIDs, including diclofenac, values of one or more liver enzymes may increase. During prolonged treatment with Diclofenac, regular monitoring of hepatic function is indicated as a precautionary measure. If abnormal liver function tests persist or worsen, if clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (e.g. eosinophilia, rash), Diclofenac should be discontinued. Hepatitis may occur with use of diclofenac without prodromal symptoms.

Caution is called for when using Diclofenac in patients with hepatic porphyria, since it may trigger an attack.

## **Renal effects**

As fluid retention and edema have been reported in association with NSAID therapy, including diclofenac, particular caution is called for in patients with impaired cardiac or renal function, history of hypertension, the elderly, patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and in those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery (see section 4.3 Contraindications). Monitoring of renal function is recommended as a precautionary measure when using Diclofenac in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.

### **Skin reactions**

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see 4.8 Undesirable effects). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment. Diclofenac should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

As with other NSAIDs, allergic reaction including anaphylactic/anaphylactoid reactions, can also occur in rare cases with diclofenac without earlier exposure to the drug.

### **Cardiovascular and cerebrovascular effects**

Appropriate monitoring and advice are required for patients with a history of hypertension and/or congestive heart failure (NYHA-I) as fluid retention and oedema have been reported in association with NSAID therapy.

Patients with congestive heart failure (NYHA-I) and patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration and only at doses  $\leq 100\text{mg}$  daily when treatment continues for more than 4 weeks.

As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially when treatment continues for more than 4 weeks.

Patients should remain alert for the signs and symptoms of serious arteriothrombotic events (e.g. chest pain, shortness of breath, weakness, slurring of speech), which can occur without warnings. Patients should be instructed to see a physician immediately in case of such an event.

### **Hematologic effects**

During prolonged treatment with Diclofenac, as with other NSAIDs, monitoring of the blood count is recommended.

Like other NSAIDs, diclofenac may temporarily inhibit platelet aggregation. Patients with defects of haemostasis should be carefully monitored.

### **Respiratory effects (pre-existing asthma)**

In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary diseases 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 edema or urticaria are more frequent than in other patients. Therefore, special caution is recommended in such patients (readiness for emergency). This is applicable as well for patients who are allergic to other substances, e.g. with skin reactions, pruritus or urticaria.

### **Geriatric patients**

Caution is indicated in the elderly on basic medical grounds especially used in frail elderly patients or those with a low body weight.

### **Interactions with NSAIDs**

The concomitant use of Diclofenac with systemic NSAIDs including cyclooxygenase-2 selective inhibitors, should be avoided due to undesirable effects (see section 4.5 Interactions with other medicinal products and other forms of interactions).

### **Masking signs of infections**

Like other NSAIDs, diclofenac may mask the signs and symptoms of infection due to its pharmacodynamic properties.

## **4.5 Interaction with other medicinal products and other forms of interaction**

The following interactions include those observed with Diclofenac gastro-resistant tablets and/or other pharmaceutical forms of diclofenac.

### **Observed interactions to be considered**

**CYP2C9 inhibitors:** Caution is recommended when co-prescribing diclofenac with CYP2C9 inhibitors (such as sulfapyridine and voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac. **Lithium:** If used concomitantly, diclofenac may raise plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.

**Digoxin:** If used concomitantly, diclofenac may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

**Diuretics and antihypertensive agents:** Like other NSAIDs, concomitant use of diclofenac with diuretics or antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect. Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity. (See section 4.4 Special warnings and special precautions for use)

**Cyclosporine and tacrolimus:** Diclofenac, like other NSAIDs, may increase the nephrotoxicity of cyclosporin and tacrolimus due to the effect on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving cyclosporin and tacrolimus.

**Drugs known to cause hyperkalemia:** Concomitant treatment with potassium-sparing diuretics, cyclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should therefore be monitored frequently (see section 4.4 Warnings and precautions).

**Quinolone Antibacterials:** There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs.

#### **Anticipated interactions to be considered**

**Other NSAIDs and corticosteroids:** Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects (see section 4.4 Special warnings and special precautions for use)

**Anticoagulants and anti-platelet agents:** Caution is recommended since concomitant administration could increase the risk of bleeding (see section 4.4 Special warnings and precautions for use). Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.

**Selective serotonin reuptake inhibitors (SSRIs):** Concomitant administration of systemic NSAIDs, including diclofenac, and SSRIs may increase the risk of gastrointestinal bleeding (see section 4.4 Special warnings and precautions for use).

**Antidiabetics:** Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of both hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

There have also been isolated reports of metabolic acidosis when diclofenac was co-administered with metformin, especially in patients with pre-existing renal impairment.

**Phenytoin:** When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin.

**Methotrexate:** Diclofenac can inhibit the tubular renal clearance of methotrexate hereby increasing methotrexate levels. Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before or after treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased.

**Colestipol and Cholestyramine:** These agents can induce a delay or decrease in absorption of diclofenac. Therefore, it is recommended to administer diclofenac at least one hour before or 4 to 6 hours after administration of colestipol/ Cholestyramine.

**CYP2C9 inducers:** Caution is recommended when co-prescribing diclofenac with CYP2C9 inducers (such as rifampicin), which could result in a significant decrease in plasma concentration and exposure to diclofenac).

#### **4.6 Fertility, pregnancy and lactation**

##### **Fertility**

There are no data to suggest any recommendations for women of child-bearing potential.

##### **Pregnancy**

There are insufficient data on the use of diclofenac in pregnant women. Some epidemiological studies suggest an increased risk of miscarriage after use of a prostaglandin synthesis inhibitor (such as NSAIDs) in early pregnancy, however the overall data are inconclusive.

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %.

The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality.

In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, Diclofenac should not be given unless clearly necessary. If Diclofenac is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- Renal dysfunction, which may progress to renal failure with oligo-hydroamniosis; the mother and the neonate, at the end of pregnancy, to:
- Possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- Inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, Diclofenac is contraindicated during the third trimester of pregnancy.

##### **Lactation**

Like other NSAIDs, diclofenac passes into the breast milk in small amounts. Therefore, Diclofenac should not be administered during breastfeeding in order to avoid undesirable effects in the infant.

##### **Fertility**

As with other NSAIDs, the use of Diclofenac may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Diclofenac

should be considered.

#### 4.7 Effects on ability to drive and use machines

Not relevant

#### 4.8 Undesirable effects

Adverse drug reactions from clinical trials and/or spontaneous or literature cases (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (>1/10); common ( $\geq 1/100$ , <1/10); uncommon ( $\geq 1/1,000$ , <1/100); rare ( $\geq 1/10,000$ , <1/1,000); very rare (<1/10,000), not known: cannot be estimated from the available data.

The following undesirable effects include those reported with Diclofenac gastro-resistant tablets and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use.

**Table 1**

<b>Blood and lymphatic system disorders</b>	
Very rare:	Thrombocytopenia, leukopenia, anemia (including hemolytic and aplastic anemia), agranulocytosis.
<b>Immune system disorders</b>	
Rare:	Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and
Very rare:	Angioedema (including face oedema).
<b>Psychiatric disorders</b>	
Very rare:	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.
<b>Nervous system disorders</b>	
Common:	Headache, dizziness.
Rare:	Somnolence.
Very rare:	Paresthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, dysgeusia, cerebrovascular
<b>Eye disorders</b>	
Very rare:	Visual impairment, blurred vision, diplopia.
<b>Ear and labyrinth disorders</b>	
Common:	Vertigo.
Very rare:	Tinnitus, impaired hearing.
<b>Cardiac disorders</b>	
Uncommon*: Frequency not	Myocardial infarction, cardiac failure, palpitations, chest pain. Kounis Syndrome
<b>Vascular disorders</b>	
Very rare:	Hypertension, vasculitis.
<b>Respiratory, thoracic and mediastinal disorders</b>	
Rare:	Asthma (including dyspnea).
Very rare:	Pneumonitis.

<b>Gastrointestinal Disorders</b>	
Common	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, decreased appetite
Rare	Gastritis, gastrointestinal hemorrhage, hematemesis, haemorrhagic diarrhoea, melena, gastrointestinal ulcer (with or without bleeding gastrointestinal stenosis or perforation which may lead to peritonitis).
Very rare	Colitis (including hemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, esophageal disorder, intestinal diaphragm disease, pancreatitis.
Not known	Ischemic colitis
<b>Hepatobiliary disorder</b>	
Common	Transaminases increased.
Rare	Hepatitis, jaundice, liver disorder.
Very rare	Fulminant Hepatitis, hepatic necrosis, hepatic failure.
<b>Skin and Subcutaneous tissue disorders</b>	
Common	Rash.
Rare	Urticaria.
Very rare	Bullous dermatitis, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), exfoliative dermatitis, alopecia, photosensitivity reaction, purpura, Henoch-Schonlein purpura, pruritus.
<b>Renal and urinary disorders</b>	
Very rare	Acute kidney injury (acute renal failure), hematuria, proteinuria, nephrotic syndrome, tubulointerstitial nephritis, renal papillary necrosis.
<b>General disorders and administration site conditions</b>	
Rare	Edema.

\*The frequency reflects data from long-term treatment with a high dose (150mg/day).

## **Description of Selected adverse drug Reactions**

### **Arteriothrombotic events**

Clinical trial and epidemiological data consistently point towards an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, particularly at high dose (150mg daily) and in long term treatment (see section 4.3 and 4.4 for Contraindications and Special Warnings and precautions for use).

### **Visual effects**

Visual disturbances such as visual impairment, blurred vision or diplopia appear to be NSAID class effects and are usually reversible on discontinuation. A likely mechanism for the visual disturbances is the inhibition of prostaglandin synthesis and other related compounds that alter the regulation of retinal blood flow resulting in potential changes in vision. If such symptoms occur during diclofenac treatment, an ophthalmological examination may be considered to exclude other causes.

#### Reporting of suspected adverse reactions

The reporting of suspected adverse reactions after authorization of the medicinal product is important. It allows continuous monitoring of the benefit/ risk ratio of the medicinal product. Health professionals report any suspected adverse effects report to website: [www.zimlab.in](http://www.zimlab.in)

## **4.9 Overdose**

### **Symptoms**

There is no typical clinical picture resulting from diclofenac overdosage. Overdosage can cause symptoms such as vomiting, gastrointestinal hemorrhage, diarrhoea, dizziness, tinnitus or convulsions. In the event of significant poisoning, acute renal failure and liver damage are possible.

### **Therapeutic measures**

Management of acute poisoning with NSAIDs, including diclofenac, essentially consists of supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression.

Special measures such as forced diuresis, dialysis or hemoperfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to the high protein binding and extensive metabolism.

Activated charcoal may be considered after ingestion of a potentially toxic overdose, and gastric decontamination (e.g. vomiting, gastric lavage) after ingestion of a potentially life-threatening overdose.

## **5. Pharmacological Properties**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids, acetic acid derivatives and related substances (ATC code: M01A B05).

There is limited clinical trial experience of the use of diclofenac in JRA/ juvenile idiopathic arthritis (JIA) paediatric patients. In a randomised, double blind, 2-week, parallel group study in children aged 3-15 years with JRA/JIA, the efficacy and safety of daily 2-3mg/kg BW diclofenac was compared with acetylsalicylic acid (ASS, 50-100mg/kg BW/d) and placebo- 15 patients in each group. In the global evaluation, 11 of 15 diclofenac patients, 6 of 12 aspirin and 4 of 15 placebo patients showed improvement with the difference being statistically significant ( $p < 0.05$ ). The number of tender joints decreased with diclofenac and ASS but increased with placebo. In a second randomised, double-blind, 6-week, parallel group study in children age 4-15 years with JRA/JIA, the efficacy of diclofenac (daily dose 2-3mg/kg BW, n=22) was comparable with that of indomethacin (daily dose 2-3 mg/kg BW, n=23).

### **Mechanism of action (MOA)**

Diclofenac contains diclofenac sodium, a non-steroidal compound with pronounced antirheumatic, anti-inflammatory, analgesic and antipyretic properties. Inhibition of prostaglandin biosynthesis, which has been demonstrated in experiments, is considered fundamental to its mechanism of action. Prostaglandins play a major role in causing inflammation, pain and fever.

Diclofenac sodium in vitro does not suppress proteoglycan biosynthesis in cartilage at

concentrations equivalent to those reached in humans.

### **Pharmacodynamic effects**

In rheumatic diseases, the anti-inflammatory and analgesic properties of Diclofenac elicit a clinical response characterized by marked relief from signs and symptoms such as pain at rest, pain on movement, morning stiffness, and swelling of the joints, as well as by an improvement in function.

In post-traumatic and post-operative inflammatory conditions, Diclofenac rapidly relieves both spontaneous pain and pain on movement and reduces inflammatory swelling and wound edema.

In clinical trials Diclofenac has also been found to exert a pronounced analgesic effect in moderate and severe pain of non-rheumatic origin. Clinical studies have also revealed that, in primary dysmenorrhoea, Diclofenac is capable of relieving the pain and reducing the extent of bleeding.

## **5.2 Pharmacokinetic properties**

### **Absorption**

Diclofenac is completely absorbed from the gastro-resistant tablets after their passage through the stomach. Although absorption is rapid, its onset may be delayed due to the gastro-resistant coating of the tablet.

Mean peak plasma concentrations of 1.5 micrograms/mL (5 micro mol/L) are attained on average 2 hours after ingestion of one tablet of 50 mg. The passage of a tablet through the stomach is slower when ingested with or after a meal than when it is taken before a meal, but the amount of diclofenac absorbed remains the same.

Since about half of diclofenac is metabolised during its first passage through the liver ("first pass" effect), the area under the concentration curve (AUC) following oral or rectal administration is about half that following an equivalent parenteral dose.

Pharmacokinetic behaviour does not change after repeated administration. No accumulation occurs provided the recommended dosage intervals are observed.

The plasma concentrations attained in children given equivalent doses (mg/kg body weight) are similar to those obtained in adults.

### **Distribution**

99.7% of diclofenac is bound to serum proteins, mainly to albumin (99.4%). The apparent volume of distribution calculated is 0.12 to 0.17 L/kg.

Diclofenac enters the synovial fluid, where maximum concentrations are measured 2 to 4 hours after peak plasma values have been attained. The apparent half-life for elimination from the synovial fluid is 3 to 6 hours. Two hours after reaching peak plasma values, concentrations of the active substance are already higher in the synovial fluid than in the plasma, and they remain higher for up to 12 hours.

Diclofenac was detected in a low concentration (100 ng/mL) in breast milk in one nursing mother. The estimated amount ingested by an infant consuming breast milk is equivalent to a 0.03 mg/kg/day dose.

### **Biotransformation/metabolism**

Biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites (3'-hydroxy-,4'-hydroxy-,5-hydroxy-,4',5-dihydroxy- and 3'-hydroxy-4'-methoxy-diclofenac), most of which are converted to glucuronide conjugates. Two of these phenolic metabolites are biologically active, but to a much smaller extent

than diclofenac.

### **Elimination**

Total systemic clearance of diclofenac from plasma is 263  $\pm$  56 mL/min (mean value  $\pm$  SD). The terminal half-life in plasma is 1 to 2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1 to 3 hours. One metabolite, 3'-hydroxy- 4'-methoxy-diclofenac has a much longer plasma half-life. However, this metabolite is virtually inactive.

About 60% of the administered dose is excreted in the urine as the glucuronide conjugate of the intact molecule and as metabolites, most of which are also converted to glucuronide conjugates. Less than 1% is excreted as unchanged substance. The rest of the dose is eliminated as metabolites through the bile in the faeces.

### **Linearity/non-linearity**

The amount absorbed is linearly related to the size of the dose.

### **Special populations**

Geriatric patients: No relevant age-dependent differences in the drug's absorption, metabolism or excretion have been observed.

Renal impairment: In patients suffering from renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics when applying the usual dosage schedule. At a creatinine clearance of <10 mL/min, the calculated steady-state plasma levels of the hydroxy metabolites are about 4 times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile.

Hepatic impairment: In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

Diclofenac is a well-established product.

## **5.3 Preclinical safety data**

Preclinical data from acute and repeated dose toxicity studies, as well as from genotoxicity, mutagenicity, and carcinogenicity studies with diclofenac revealed no specific hazard for humans at the intended therapeutic doses. In standard preclinical animal studies, there was no evidence that diclofenac had a teratogenic potential in mice, rats or rabbits.

Diclofenac had no influence on the fertility of parent animals in rats. Except for minimal fetal effects at maternally toxic doses, the prenatal, perinatal and postnatal development of the offspring was not affected.

Administration of NSAIDs (including diclofenac) inhibited ovulation in the rabbit and implantation and placentation in the rat, and led to premature closure of the ductus arteriosus in the pregnant rat. Maternally toxic doses of diclofenac were associated with dystocia, prolonged gestation, decreased fetal survival, and intrauterine growth retardation in rats. The slight effects of diclofenac on reproduction parameters and delivery as well as constriction of the ductus arteriosus in utero are pharmacologic consequences of this class of prostaglandin synthesis inhibitors (see sections 4.3 Contraindications and 4.6 Fertility, pregnancy and breast-feeding).

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Tablet Core:

Maize Starch  
Microcrystalline Cellulose  
Sodium Starch Glycolate (Type-A)  
Calcium Hydrogen Phosphate  
Colloidal Anhydrous Silica  
Povidone  
Polyethylene Glycol  
Magnesium Stearate  
Purified talc

Tablet Coat:  
Opadry Blue  
Purified water

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

3 years

**6.4 Special precautions for storage**

Store at a temperature not exceeding 30°C, protect from light and moisture.

**6.5 Nature and contents of container**

10 x 10 Tablets Alu- PVC Blister Pack

**6.6 Special precautions for disposal**

No special requirements.

**7. MARKETING AUTHORISATION HOLDER**

Zim Laboratories Limited.  
Sadoday Gyan (Ground Floor),  
Opp. NADT, Nelson Square,  
Nagpur – 440013  
India.

**8. MARKETING AUTHORISATION NUMBER(S)**

06977/08191/REN/2021

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

28/12/2021

**10. DATE OF REVISION OF THE TEXT**

04/07/2023