# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Declophen Fast

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Sachet contains 50 mg diclofenac potassium. For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Granules for oral solution

White granular powder giving translucent solution after reconstitution.

The pH of the reconstituted solution is 6.5 - 8.5.

## 4. CLINICAL PARTICULARS

### 4.1.Therapeutic indications

Declophen Fast is indicated as short-term treatment in the following acute conditions:

-Post- traumatic pain, inflammation and swelling, e.g. due to sprains.

- Post-operative pain, inflammation and swelling, e.g. following dental or orthopaedic surgery.

- Painful and/or inflammatory conditions in gynaecology, e.g. primary dysmenorrhoea or adnexitis.

- Migraine attacks.

- Painful syndromes of the vertebral column.

- Non-articular rheumatism.

- As adjuvant in severe painful inflammatory infections of the ear, nose, or throat, e.g. pharyngo- tonsillitis, otitis. In keeping with general therapeutic principles, the underlying disease should be treated with basic therapy, as appropriate. Fever alone is not an indication.

**4.2 Posology and method of administration**

Declophen Fast should only be prescribed when the benefits are considered to outweigh the potential risks. After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest possible duration should be used. Adverse effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms.
The contents of the sachet should be dissolved with stirring in a glass of natural (non-carbonated) water. The solution may remain slightly opalescent, but this should not influence the efficacy of the preparation. The solution should be swallowed preferably before meals.

**General target population**
The recommended initial daily dose is 100 to 150 mg (2 – 3 sachets). In milder cases, 50 to 100 mg (1 – 2 sachets) daily are usually sufficient. The daily dose should generally be divided in up to 3 doses. In primary dysmenorrhoea, the daily dose should be individually adjusted and is generally 50 to 150 mg (1 – 3 sachets). A dose of 50 to 100 mg (1 – 2 sachets) should be given initially and, if necessary increased over the course of several menstrual cycles up to a total maximum of 200 mg (4 sachets) daily. Treatment should be started on appearance of the first symptoms and, depending on the symptomatology, continued for a few days.

In migraine, an initial dose of 50 mg (1 sachet) should be taken at the first signs of an impending attack. In cases where pain relief within 2 hours after the first dose is not sufficient, a further dose of 50 mg may be taken. If needed, further doses of 50 mg (1 sachet) may be taken at intervals of 4 to 6 hours, not
exceeding a total dose of 200 mg (4 sachets) per day.

**Special population Paediatrics**

Declophen Fast Granules for Oral Solution is not recommended for use in children and adolescents below 14 years of age. For treatment in children and adolescents below 14 years of age, other forms of diclofenac are available.

*For adolescents aged 14 years and over:* 50 to 100 mg (1 – 2 sachets) daily are usually sufficient, given as 1 to 2 divided doses.

The maximum daily dose of 150 mg (3 sachets) should not be exceeded.

The use of Declophen Fast Granules for Oral Solution in migraine attacks has not been established in children and adolescents.

**Geriatrics (Patients aged 65 or above)**

No adjustment of the starting dose is required for elderly patients.

**Renal impairment**

Declophen Fast Granules for Oral Solution is contraindicated in patients with renal failure.

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 Declophen Fast Granules for Oral Solution to patients with mild to moderate hepatic adjustment.

**Hepatic impairment**

Declophen Fast Granules for Oral Solution is contraindicated in patients with hepatic failure.

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 Declophen Fast Granules for Oral Solution to patients with mild to moderate hepatic impairment.

## 4.3 Contraindications

-Known hypersensitivity to the active substance or any of the excipients.

-Active gastric or intestinal ulcer, bleeding or perforation.

-Last trimester of pregnancy.

-Severe hepatic, renal or cardiac failure.

-Like other non-steroidal anti-inflammatory drugs (NSAIDs), Declophen Fast Granules for Oral Solution is contraindicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetyl-salicylic acid or other NSAIDs.

## 4.4 Special warnings and precautions for use

***Warnings***

**Cardiovascular Risk*:** NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke.This risk may increase with duration of use. Patients with cardiovascular diseases or risk factors for cardiovascular diseases may be at greater risk. NSAIDs is contraindicated for the treatment of peri-operative pain in the setting of coronary artery by pass graft (CABG) surgery.

Patients with previous myocardial infarction (within the last 6 to 12 months) should not use diclofenac. Treatment with Declophen Fast is generally not recommended in patients with established cardiovascular disease (e.g, congestive heart failure, established ischaemic heart disease or peripheral arterial disease) or uncontrolled hypertension. If needed, patients with established cardiovascular disease, uncontrolled hypertension or significant risk factors for cardiovascular disease (e.g. hypertension, hyperlipidemia, diabetes mellitus and smoking) should be treated with Declophen Fast only after careful consideration and only at doses ≤ 100 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 lowest effective dose should be used for the shortest duration possible.

The patient's need for symptomatic relief and response to therapy should be reevaluated periodically, especially when treatment continues for more than 4 weeks.

Prescribers should inform the individual patient of the possible increased when prescribing diclofenac for patients at high risk of cardiovascular events.

Physicians and patients should remain alert for such events, even in the absence of previous cardiovascular symptoms. Patients should be informed about the signs and/or symptoms of cardiovascular toxicity and the steps to take should they occur.

Patients should remain alert for the signs and symptoms of serious arteriothrombotic events (e.g. chest pain, shortness of breath, weakness, slurring speech), which can occur without warning.

Patients should be instructed to see a physician immediately in case of such an event.

There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAIDs use.

**Gastrointestinal Risk*:** NSAIDs cause an increased risk of serious gastrointestinal adverse events including inflammation, bleeding, ulceration and perforation of the stomach or intestine. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

Upper GI ulcers, gross bleeding or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months and in about 2 – 4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy, However, even short-term therapy is not without risk.

Caution is advised in patients with risk factors for gastrointestinal events who may be at greater risk of developing serious gastrointestinal events, e.g. the elderly, those with a history of serious gastrointestinal events, smoking and alcoholism.

The concurrent use of aspirin and NSAIDs also increases the risk of serious gastrointestinal adverse events.

Doctors should warn patients about the signs and symptoms of serious gastrointestinal toxicity.
**Hypertension:** NSAIDs may lead to the onset of new hypertension or worsening of pre-existing hypertension and patients taking anti-hypertensives with NSAIDs may have an impaired anti- hypertensive response.

Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

**Heart failure:** Fluid retention and oedema have been observed in some patients taking NSAIDs, therefore caution is advised in patients with fluid retention or heart failure.

**Severe skin reactions:** Serious skin reactions, some of them fatal, including exfoliative dermatitis. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TENS), have been reported very rarely in association with the use of NSAIDs, including Declophen Fast Granules for Oral Solution. These serious adverse events are idiosyncratic and are independent of dose or duration of use. Patients appear to be at highest risk of these reactions in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity, and Declophen Fast Granules for Oral Solution should be discontinued.

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

Like other NSAIDs, Declophen Fast Granules for Oral Solution may mask the signs and symptoms of infection due to its pharmacodynamic properties.

This product contains sucrose, if you have been told by your doctor that you have intolerance to some sugars contact your doctor before taking this product.

**Precautions**

**Geriatrics:** Caution is indicated in the elderly on basic medical grounds. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight.

**Interactions with other NSAIDs**

The concomitant use of Declophen Fast Granules for Oral Solution with systemic NSAIDs including cyclooxgenase-2 selective inhibitors, should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse effects.

Caution is indicated in the elderly on basic medical grounds. In particular it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight.

Declophen Fast Granules for Oral Solution contains aspartame as a source of phenylalanine and may be therefore harmful for patients with phenylketonuria.

**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 oedema or urticaria are more frequent than in other patients. Therefore, special precaution 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.

**Gastrointestinal effects**

As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be exercised when prescribing Declophen Fast Granules for Oral Solution in patients with symptoms indicative of gastrointestinal (GI) disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation. 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 and in the elderly.

To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with haemorrhage 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 medicinal products containing low-dose acetylsalicylic acid (ASA)/aspirin or other medicinal products likely to increase gastrointestinal risk.

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially of 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. Close medical surveillance and caution should be exercised in patients with ulcerative colitis or Crohn's disease as their condition may be exacerbated.

**Hepatic effects**

Close medical surveillance is required when prescribing Declophen Fast Granules for Oral Solution 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 Declophen Fast Granules for Oral Solution, 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), Declophen Fast Granules for Oral Solution should be discontinued. Hepatitis may occur with use of diclofenac without prodromal symptoms.

Caution is called for when using Declophen Fast Granules for Oral Solution in patients with hepatic porphyria, since it may trigger an attack.

**Renal effects**

As fluid retention and oedema 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 extracelluar volume depletion from any cause, e.g. before and after major surgery. Monitoring of renal function is recommended as a precautionary measure when using Declophen Fast Granules for Oral Solution in such cases. Discontinuation of therapy is normally followed by a recovery to the pre-treatment state.

**Haematological effects**

Use of Declophen Fast Granules for Oral Solution is recommended only for short-term treatment. If however, Declophen Fast Granules for Oral Solution is used for a prolonged period, monitoring of the blood count is recommended, as with other NSAIDs.

Like other NSAIDs, Declophen Fast Granules for Oral Solution may temporarily inhibit platelet aggregation. Patients with defects of hemostasis should be carefully monitored.

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

The following interactions include those observed with Declophen Fast Granules for Oral Solution and/or other pharmaceutical forms of diclofenac.

*Observed interactions to be considered*

***Potent CYP2C9 inhibitors:*** Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as sulfinpyrazone and voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism.

***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.

***Other NSAIDs and corticosteroids:*** Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal adverse effects.

***Anticoagulants and anti-platelet agents:*** Caution is recommended since concomitant administration could increase the risk of bleeding. Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are isolated 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.

***Antidiabetics:*** 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.

***Methotrexate:*** 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.

***Cyclosporin:*** Diclofenac, like other NSAIDs, may increase the nephtotoxicity of cyclosporin 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.

***Drugs known to cause hyperkalemia:*** Concomitant treatment with potassium-sparing diuretics, cyclosporin, tacrolimus or trimethoprin may be associated with increased serum potassium levels, which should therefore be monitored frequently.

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

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

**4.6 Fertility, Pregnancy and lactation**

Women of child-bearing potential

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. Therefore, Declophen Fast Granules for Oral Solution should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the foetus. As with other NSAIDs, use of diclofenac during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia and/or premature closure of the ductus arteriosus.

**Breast-feeding**

Like other NSAIDs, diclofenac passes into the breast milk in small amounts. Therefore, Declophen Fast Granules for Oral Solution should be administered during breast feeding in order to avoid adverse effects in the infant.

**Fertility**

As with other NSAIDs, the use of Declophen Fast Granules for Oral Solution 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 Declophen Fast Granules for Oral Solution should be considered.

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

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be advised that they may experience undesirable effects such as dizziness, accommodation disorder, mydriasis and blurred vision during the treatment with Declophen Fast Granules for Oral Solution. If patients experience the above-mentioned side effects, they should avoid potentially hazardous tasks such as driving or operating machines.

**4.8 Undesirable effects**

The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (>1/10); common (≥ 1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000). The following adverse effects include those reported with Declophen Fast Granules for Oral Solution and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use.

**Blood and lymphatic system disorders**

Very rare: Thrombocytopnia, leucopenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis.

**Immune system disorders**

Rare: Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock). Very rare: Angioedema (including face oedema).

**Psychiatric disorders**

Very rare: Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.

**Nervous system disorders** Common: Headache, dizziness Rare: Somnolence.

Very rare: Paraesthesia, memory impairment, convulsion, anxiety, tremor, meningitis aseptic, dysgeusia, cerebrovascular accident.

**Eye disorders**

Very rare: Visual impairment, vision blurred, diplopia.

**Ear and labyrinth disorders**

Common: Vertigo.

Very rare: Tinnitus, hearing impaired.

**Cardiac disorders**

Uncommon: Cardiac failure, myocardial infarction, palpitations, chest pain.

**Vascular disorders**

Very rare: Hypertension, vasculitis.

**Respiratory, thoracic and mediastinal disorders**

Rare: Asthma (including dyspnoea). Very rare: Pneumonitis.

**Gastrointestinal disorders**

Common: Nausea, vomiting, diarrhea, dyspepsia, abdominal pain, flatulence, decreased appetite.

Rare: Gastritis, gastrointestinal haemorrhage, haematemesis, melaena, diarrhea hemorrhagic, gastrointestinal ulcer (with or without bleeding or perforation).

Very rare: Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, oesophageal disorder, intestinal diaphragm disease, pancreatitis.

**Hepatobiliary disorders**

Common: Transaminases increased. Rare: Hepatitis, jaundice, liver disorder. Very rare: Hepatitis fulminant,

hepatic necrosis, hepatic failure.

**Skin and subcutaneous tissue disorders**

Common: Rash. Rare: Urticaria.

Very rare: Dermatitis bullous, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, alopecia, photosensitivity reaction, Henoch-Schonlein purpura, pruritus.

**Renal and urinary disorders**

Very rare: Renal failure acute, haematuria, proteinuria, nephritic syndrome, tubulointerstitial nephritis, renal papillary necrosis.

**General disorders and administration site conditions**

Rare: Oedema.

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

**Description of selected adverse drug reactions Arteriothrombotic events:**

Meta-analysis and pharmacoepidemiological data point towards a small increased risk of arteriothrombotic events (for example myocardial infarction) associated with the use of diclofenac, particularly at a high dose (150 mg daily) and during long-term treatment.

**4.9 Overdose Symptoms**

There is no typical clinical picture resulting from diclofenac overdosage. Overdosage can cause symptoms such as vomiting, gastrointestinal haemorrhage, diarrhea, 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 haemoperfusion 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.

Declophen Fast Granules for Oral Solution contains the potassium salt of diclofenac, a non- steroidal compound with pronounced analgesic, anti-inflammatory, and antipyretic properties.

Declophen Fast Granules for Oral Solution has a rapid onset of action, which makes it particularly suitable for the treatment of acute painful and inflammatory conditions. Inhibition of prostaglandin

biosynthesis, which has been demonstrated in experiments, is considered to be fundamental to its mechanism of action.

Prostaglandins play a major role in causing inflammation, pain, and fever.

Diclofenac potassium *in vitro* does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in humans.

***Pharmacodymanics***

Diclofenac has been found to exert a pronounced analgesic effect in moderate and severe pain. In the presence of inflammation, e.g. due to trauma or following surgical interventions, it rapidly relieves both spontaneous pain and pain on movement and diminishes inflammatory swelling and wound oedema.

Clinical trials have also revealed that in primary dysmenorrhoea the active substance is capable of relieving the pain and reducing the extent of bleeding. In migraine attacks diclofenac has been shown to be effective in relieving the headache and in improving the accompanying symptoms nausea and vomiting.

**5.2 Pharmacokinetic properties Absorption**

Diclofenac is rapidly and completely absorbed from diclofenac potassium. Mean peak plasma concentrations of 5.5 micromol/L are attained after 5 to 20 minutes after ingestion of one sachet of 50 mg.

Ingestion together with food is expected to have no influence on the amount of diclofenac absorbed although onset and rate of absorption may be slightly delayed.

Since about half of diclofenac is metabolized during its first passage through the liver (“first pass”effect), the area under the concentration curve (AUC) is about half as large following oral or rectal administration as it is following a parenteral dose of equal size.

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

**Distribution**

99.7% of diclofenac binds 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 reached. The apparent half-life for elimination from the synovial fluid is 3 to 6 hours. Two hours after reaching peak plasma levels, 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 0.03 mg/kg/day dose.

**Biotransformation/metabolism**

Biotransformation of diclofenac takes partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several metabolites, most of which are converted to glucuronide conjugates. Two of these phenolic metabolites are biologically active, but to a much lesser 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 in linear proportion to the size of the dose.

**Special population**

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

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

## 6. PHARMACEUTICAL PARTICULARS

**6.1. List of excipients** Potassium bicarbonate, Aspartame,

Saccharine sodium , Anise powder flavour,

Peppermint powder flavour , Sucrose.

**6.2. Incompatibilities**

Not Applicable

**6.3. Shelf life**

24 months.

**6.4. Special precautions for storage**

Store at temperature not exceeding 30°C, in a dry place

**6.5. Nature and contents of container**

A carton box containing 10 aluminium laminated foil sachets each consists of 4 layers (LDPE-Al- LDPE-PAPER), each containing 2 g and insert leaflet.

## 7. Marketing Authorization Holder

Pharco Pharmaceutical

## 8. MARKETING AUTHORISATION NUMBER(S)

26729/2010

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

02/06/2016

## 10. DATE OF REVISION OF THE TEXT

January 2023.