Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

TOFLA (Diclofenac Sodium Oral Suspension 1.8 mg/mL)

2. Qualitative and quantitative composition

Each ml contains:

Diclofenac Sodium BP 1.8 mg

In a flavoured syrupy base - Q.S.

Colour: Sunset Yellow

Excipients of known effect

Sucrose

Methylene paraben

Sunset Yellow

Refers to Section 6.1 for full excipient list

3. Pharmaceutical form

Orange coloured suspension

4. Clinical particulars

4.1 Therapeutic indications

Diclofenac sodium may be prescribed to children for conditions like juvenile idiopathic arthritis or postoperative pain, under close medical supervision.

4.2 Posology and method of administration

Use in Paediatric patients (below 18 years of age)

Age	**Dose**	**Frequency**	**Max Daily Dose**
1–4 years	1 mg/kg/dose	q8h	3 mg/kg/day
5–12 years	0.75 mg/kg/dose	q12h	2.25 mg/kg/day
>12 years	Adult dosing	-	75 mL/day

Reduce dose by 25% in children with **mild hepatic impairment** (Child-Pugh A)

Avoid in **severe renal impairment** (eGFR <30 mL/min/1.73m²)

Diclofenac oral suspension is particularly suitable for paediatric use, because they enable the dose to be adopted individually to the child's body weight in accordance with the dosage schedule recommended for children.

Children aged 1 year or over and adolescents should be given 0.25 to 1ml/kg body weight, daily, depending on the severity of the disorder. (1mg/kg to 3mg/kg a day given in divided doses).

For adolescents aged 14 or over, 37.5 to 50ml daily is usually sufficient. The total daily dose should generally be divided into 2 to 3 separate doses. The maximum daily dose of 75ml should not be exceeded.

Adults

Specific pharmaceutical forms (e.g. tablets, suppositories, solution for injection) are available that are more suitable for use in adults. The initial daily dose is 50ml to 75ml. in milder cases, 37.5 to 50ml daily is usually sufficient.

The total daily dose should generally be divided into 2 to 3 separate doses. The maximum daily dose of 75ml should not be exceeded.

Special populations

Elderly

Although the pharmacokinetics of Diclofenac sodium are not impaired to any clinically relevant extent in elderly patients, non-steroidal anti-inflammatory drugs (NSAIDs) should be used with caution in such patients who generally are more prone to adverse reactions. It is recommended that the lowest effective dosage be used in frail elderly patients or those with a low body weight (see also precautions) and the patient should be monitored for GI bleeding during NSAID therapy.

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.

Renal impairment

Diclofenac is contraindicated in patients with severe renal impairment. 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 mild to moderate renal impairment.

Method of administration: For oral administration.

The oral suspension should be swallowed preferably before meals or on am empty stomach.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients used in formulation.

Active, or gastric or intestinal ulcer, bleeding or perforation.
History of gastrointestinal bleeding or perforation, relating 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

Hepatic failure

Renal failure
Established congestive heart failure (NYHA-II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
Like other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac is also contraindicated in patients in whom attacks of asthma, angioedema, urticarial or acute rhinitis are precipitated by ibuprofen, acetylsalicylic acid or other nonsteroidal anti-inflammatory drugs.

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. The concomitant use of diclofenac sodium 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. Caution is indicated in the elderly on basic medical grounds. It is

recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight. As with other nonsteroidal anti-inflammatory drugs, including diclofenac, allergic reactions, including anaphylactic/anaphylactoid reactions can also occur without earlier exposure to the drug. Like other NSAIDs, diclofenac may mask the signs and symptoms of infection due to its pharmacodynamic properties.
This medicine contains sucrose and therefore is not recommended for patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucraseisomaltase insufficiency.

Gastrointestinal effects

Gastrointestinal bleeding (hematemesis, melaena), 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 (GI) events. They generally have more serious consequences for the elderly. If gastrointestinal bleeding or ulceration occurs in patients receiving diclofenac, the medicinal product should be withdrawn. As with all NSAIDs, including diclofenac, close medical surveillance is imperative, and caution should be exercised when prescribing diclofenac in patients with symptoms indicative of gastrointestinal disorders or with history suggestive of gastric or intestinal ulceration, bleeding or perforation. The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses including diclofenac and in patients with a history of ulcer, particularly if

complicated with hemorrhage 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., misoprostol or proton pump inhibitors) 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 GI bleeding). Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors (SSRIs) or anti- platelet agents such as acetylsalicylic acid Close medical surveillance and caution should also be exercised in patients with ulcerative colitis or Crohn's disease, as their condition may be exacerbated.

Hepatic impairment

Close medical surveillance is required when prescribing diclofenac to patients with impairment

of 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, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), diclofenac should be discontinued. Hepatitis may occur with diclofenac without prodromal symptoms. Caution is called for when using diclofenac in patients with hepatic porphyria, since it may trigger an attack.

Renal impairment

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 extracellular volume depletion from any cause, e.g. before or after major surgery. 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 pretreatment state.

Skin effects

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, including diclofenac. 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 sodium should be discontinued at the first appearance of skin rash, mucosal lesions or any other signs of hypersensitivity.

SLE and mixed connective tissue disease

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis.

Cardiovascular and cerebrovascular effects

Patients with significant risk factors for cardiovascular events (e.g., hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration. 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. 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 including diclofenac. Clinical trial and epidemiological data consistently point towards 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. Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with diclofenac after careful consideration.

Haematological effects

During prolonged treatment with diclofenac, as with other NSAIDs, monitoring of the blood count is recommended. Diclofenac may reversibly inhibit platelet aggregation. Patients with defects of haemostasis, bleeding diathesis or haematological abnormalities should be carefully monitored.

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. Like other drugs that inhibit prostaglandin synthetase activity, diclofenac sodium and other NSAIDs can precipitate bronchospasm if administered to patients suffering from, or with a previous history of bronchial asthma.

Hypersensitivity Reactions

Absolute contraindication in patients with:

Aspirin-exacerbated respiratory disease (AERD) (historically called "aspirin triad"):

Asthma *and* chronic rhinosinusitis *and* nasal polyps

Risk: Bronchospasm, laryngeal oedema, or anaphylaxis within 1–6 hours

of NSAID exposure.

Cross-reactive urticaria/angioedema:

History of hives, facial swelling, or anaphylaxis after aspirin/NSAIDs.

Mechanism:

Non-selective COX-1 inhibition (by diclofenac) → upregulated leukotriene production → severe allergic-type reactions.

At-risk populations:

- 7-20% of adults with asthma
- 30-40% of patients with asthma *and* nasal polyps

Diclofenac Sodium Oral Suspension: Comprehensive Safety Profile

Risk Category	Key Considerations	At-Risk Populations	Monitoring Requirements	Risk Mitigation Strategies
General Principles	- Use lowest effective dose for shortest duration - No synergistic benefit with other NSAIDs	All patients	- Regular clinical response assessment	- Avoid combination NSAID therapy - Re-evaluate need after 3 months
Cardiovascular (Boxed Warning)	- ↑ MI/stroke risk (1.4-1.8x baseline) - Highest in first month (HR 2.65)	- Existing CVD - Hypertension - Diabetes - Smokers	- BP monitoring q2-4 weeks - CV symptom assessment	- Avoid in CABG patients - Limit duration in high-risk patients
Gastrointestinal (Boxed Warning)	- Ulcer/bleeding risk: 1-4% annually - May occur without warning	- Age >65 - H. pylori+ - Prior ulcers - Concomitant anticoagulants/steroids	- Haemoglobin checks q3-6mo - Monitor for occult blood	- PPI co-therapy for high-risk - Avoid in active GI bleeding
Hepatic	- Idiosyncratic hepatotoxicity (2–12-week latency) - ALT>AST (3:1 ratio typical)	- Chronic liver disease - Alcohol use - CYP2C9 poor metabolisers	- LFTs at baseline, 4-8 weeks, then q3mo	- Discontinue if ALT >3x ULN + symptoms - Avoid in Child-Pugh B/C cirrhosis
Renal	- Acute kidney injury risk (OR	- CKD stage ≥3 - CHF	- Serum creatinine/K+	- Hydration before

Risk Category	Key Considerations	At-Risk Populations	Monitoring Requirements	Risk Mitigation Strategies
	4.1 in volume depletion) - Hyperkalaemia	- Diuretic use - ACEi/ARB therapy	at baseline and q3mo	initiation - Avoid in eGFR <30 mL/min
Hypersensitivity	- AERD (94% cross-reactivity) - SJS/TEN (1–4-week onset)	- Asthma + nasal polyps - Prior NSAID reactions - HLA-B*1502 carriers	- Skin/mucosa inspection for first 4 weeks	- Contraindicate in AERD - Immediate discontinuation for any rash
Special Populations				
- **Elderly (≥65)**	- 20% higher AUC - Protein binding ↓ to 98.5%	- Frail elderly - Low body weight (<50 kg)	- More frequent LFTs/Cr - Fall risk assessment	- Start with 50% adult dose - Max 75 mg/day
- **Paediatrics (1-12 yrs)**	- Higher free fraction (5% vs 0.3%) - CYP2C9 immature	- Weight <15 kg - Dehydrated children	- Strict weight-based dosing - Watch for dizziness	- Max 2 mg/kg/dose - Avoid in volume depletion
Concomitant Medications				
- Anticoagulants	↑ Bleeding risk (OR 3.7)	Warfarin users	- Weekly INR checks when initiating	- Prefer alternative analgesics - If essential, use PPI + limit duration
- SSRIs	↑ GI bleeding (OR 2.4)	Fluoxetine/sertraline users	- Monitor for melena	- Pantoprazole 40 mg/day
- Diuretics	↑ Nephrotoxicity	Furosemide users	- BUN/Cr weekly first month	- Ensure euvolemia before initiation

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions include those observed with diclofenac gastro-resistant preparation and/or other pharmaceutical forms of 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 Anti-hypertensive 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 via inhibition of vasodilatory prostaglandin synthesis. 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.

Drugs known to cause hyperkalaemia: Concomitant treatment with potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should therefore be monitored frequently.

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 reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulants concomitantly. Therefore, to be certain that no change in anticoagulant dosage is required, close monitoring of such patients is required. As with other nonsteroidal anti-inflammatory agents, diclofenac in high dose can reversibly inhibit platelet

aggregation.

Other NSAIDS including cyclo-oxygenase-2selective inhibitors and corticosteroids: Coadministration of diclofenac and other systemic NSAIDs or corticosteroids may increase the risk of gastrointestinal bleeding or ulceration. Avoid concomitant use of two or more NSAIDs.

Selective serotonin reuptake inhibitors (SSRIs): Concomitant administration of SSRIs may increase the risk of gastrointestinal bleeding.

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 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: 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 treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased. Cases of serious toxicity have been reported when methotrexate and NSAIDs including diclofenac are given within 24 hours of each other. This interaction is mediated through accumulation of methotrexate resulting from impairment of renal excretion in the presence of the NSAID.

Ciclosporin: Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin 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 ciclosporin.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

This might be mediated through renal antiprostagladin effects of both NSAID and calcineurin inhibitor.

Quinolone antimicrobials: Convulsions may occur due to an interaction between quinolones and NSAIDs. This may occur in patients with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving an NSAID.

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

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.

Cardiac glycosides: Concomitant use of cardiac glycosides and NSAIDs in patients may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Potent CYP2C9 inhibitors: “Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as voriconazole), which could

result in a significant increase in peak plasma concentration and exposure to diclofenac due to inhibition of diclofenac metabolism.

4.6 Pregnancy and Lactation

Pregnancy:

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. 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-hydramnios's; 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. Use of

diclofenac may delay or prevent ovulation. Women planning pregnancy should discontinue treatment. Consequently, diclofenac sodium is contraindicated during the third trimester of pregnancy.

Breast-feeding: Like other NSAIDs, diclofenac passes into the breast milk in small amounts. Therefore, diclofenac should not be administered during breast feeding to avoid undesirable effects in the infant

Female 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

Patients who experience visual disturbances, dizziness, vertigo, somnolence central nervous system disturbances, drowsiness or fatigue while taking NSAIDs should refrain from driving or operate machinery.

4.8 Undesirable effects

Frequency	**Adverse Reaction**
Very common (≥1/10)	Nausea, abdominal pain
Common (≥1/100 to <1/10)	Headache, dizziness, vomiting
Rare (≤1/10,000)	Toxic epidermal necrolysis, Stevens-Johnson syndrome

Infections and infestations: Rhinitis

Blood and the lymphatic system disorders: Thrombocytopenia, leucopoenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis.

Immune system disorders: Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock). Angioneurotic oedema (including face oedema).

Psychiatric disorders: Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.

Nervous system disorders: Headache, dizziness, Somnolence, tiredness, Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident, Confusion, hallucinations, disturbances of sensation, malaise.

Eye disorders

Visual disturbance, vision blurred, diplopia, Optic neuritis.

Ear and labyrinth disorders

Vertigo, Tinnitus, hearing impaired.

Cardiac disorders

Myocardial infarction, cardiac failure, palpitations, chest pain.

Vascular disorders

Hypertension, hypotension, vasculitis.

Respiratory, thoracic and mediastinal disorders

Asthma (including dyspnoea), Pneumonitis.

Gastrointestinal disorders

Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia. Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer with or without bleeding or perforation (sometimes fatal particularly in the elderly). Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's

disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis. Ischaemic colitis.

Hepatobiliary disorders

Transaminases increased. Hepatitis, jaundice, liver disorder. Fulminant hepatitis, hepatic necrosis, hepatic failure.

Skin and subcutaneous tissue disorders

Rash. Urticaria. Bullous eruptions, eczema, erythema, erythema multiforme, Stevens- Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura, allergic purpura, pruritus.

Renal and urinary disorders

Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis.

Reproductive system and breast disorders

Impotence

General disorders and administration site conditions

Oedema

4.9 Overdose

May increase the risk of gastrointestinal bleeding or ulceration. Avoid concomitant use of overdose of NSAIDs.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Non-steroidal anti-inflammatory drugs (NSAlDs).

Mechanism of action: Diclofenac sodium is a non-steroidal agent with marked analgesic/anti-inflammatory properties. It is an inhibitor of prostaglandin synthetase, (cyclo-oxygenase). Diclofenac sodium in vitro does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in human beings.

5.2 Pharmacokinetic properties

Absorption

Absorption is complete but onset is delayed until passage through the stomach, which may be affected by food which delays stomach emptying. The mean peak plasma diclofenac concentration reached at about 2 hours (50mg dose produces 1511± 466 ng/ml). Administration with a high-fat meal delays absorption (Tmax prolonged by 2 hours) and reduces peak plasma concentration (Cmax decreased by 30%), though total systemic exposure (AUC) remains unchanged, requiring consistent timing relative to meals for predictable therapeutic effects.

Distribution

The active substance is 99.7% protein bound, mainly to albumin (99.4%). Diclofenac enters the synovial fluid, where maximum concentrations are measured 2-4 hours after the peak plasma values have been attained. The apparent half-life for elimination from the synovial fluid is 3-6 hours. Two hours after reaching the peak plasma values, concentrations of the active substance are already higher in the synovial fluid than they are in the plasma and remain higher for up to 12 hours. Diclofenac was detected in a low concentration (1.8 mg/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

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, most of which are converted to glucuronide conjugates. Two phenolic metabolites are biologically active, but to a much lesser extent than diclofenac.

Elimination

The total systemic clearance of diclofenac in plasma is 263 ± 56 mL/min (mean value ± SD). The terminal half-life in plasma is 1-2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1-3 hours. About 60% of the administered dose is excreted in the urine in the form of 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.

Bioavailability:

About half of the administered diclofenac is metabolised during its first passage through the liver ("first-pass" effect), the area under the concentrations curve (AUC) following oral administration is about half that following an equivalent parenteral dose. Pharmacokinetic behaviour does not change on repeated administration. Accumulation

does not occur, provided the recommended dosage intervals are observed.

In children aged 1–12 years, systemic exposure (AUC) is 20% higher than in adults at equivalent doses

5.3 Preclinical safety data

None stated

6. Pharmaceutical Particulars

6.1 List of Excipients

Di Sodium EDTA, Sucralose, Xanthan Gum, Sodium Citrate, Sugar, Methyl Paraben, Propyl Paraben, Mango Ripe Liq., Sunset Yellow, Citric Acid Anhydrous, Tween – 80, Bronopol, Colloidal Anhydrous Silica, Sodium benzoate, Acesulfame potassium, Glycerine, Purified Water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-Life

Unopened: 24 months below 25°C in original container.

After opening: Use within 3 months; do not refrigerate or freeze.

Shake vigorously for 10 seconds before each use

6.4 Special Precautions for storage

Store in a cool and dark place, Protected from light.

6.5 Nature and Content of container

120ml PER BOTTLE**.**

6.6 Special precautions for disposal and other handling

None

7. Marketing Authorization Holder

PHARMAKEN LIMITED

P.o. box 95625, Mombasa - Kenya

8. Marketing Authorization Number

CTD11660

9. Date of first authorization/renewal of the authorization

30/05/2024

10. Date of revision of the text

7/05/2025