Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Dolipar 50mg/500mg Tablets.

2. Qualitative and quantitative composition

Each film-coated tablet contains 50 mg of Diclofenac sodium and 500 mg of Paracetamol.

Excipient of known effect:
This product contains 3.15 mg of sorbitol per tablet.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet.

White to off white, round shaped, flat faced bevel edged film coated tablets with a break line on one side and plain on the other side.

The tablet can be divided into two equal doses.

4. Clinical particulars

4.1 Therapeutic indications

Dolipar is indicted for the treatment or temporary relief of mild to moderate pain from headache, myalgia, back pain, musculoskeletal pain, dental pain (e.g., toothache), dysmenorrhea, and arthralgia.

4.2 Posology and method of administration

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4). The tablets should be swallowed whole with liquid, preferably before meals, and must not be divided or chewed.

Adults
The recommended initial daily dose is 1 tablet 2 to 3 times a day.
The total daily dose should generally be divided in 2 to 3 doses and must never exceed 3 tablets in a day.

In migraine, an initial dose 1 tablet should be taken at the first signs of an impending attack.

Elderly Patients
Non-steroidal anti-inflammatory drugs should be used with particular caution in frail elderly patients or those with a low body weight. In particular, it is recommended that the lowest effective dosage be used

in these patients (see section 4.4). Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or if intolerance occurs.

Renal impairment
Diclofenac is contraindicated in patients with severe renal impairment (see section 4.3). 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 (see section 4.3 and 4.4).

Hepatic impairment
Diclofenac is contraindicated in patients with severe hepatic impairment (see section 4.3). 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 impairment (see section 4.3 and 4.4).

4.3 Contraindications

- Treatment of peri-operative pain in the setting of coronary artery bypass graft surgery (CABG).
- Patients with a history of or active GI disease, including peptic ulcer disease or GI bleeding.
- Known hypersensitivity to the active substance or to any of the excipients.
- Last trimester of pregnancy.
- Hepatic failure.
- Chronic kidney disease Grade 5.
- Established congestive heart failure (NYHA II-IV), ischemic heart disease and/or cerebrovascular disease.
- Patients in whom use of acetylsalicylic acid or other NSAIDs can precipitate asthma, angioedema, urticaria, or acute rhinitis.

4.4 Special warnings and precautions for use

General

Undesirable effects may be minimised by using the lowest effective dose for the shortest possible duration necessary to control symptoms (see section 4.2 Posology and GI and cardiovascular risks below).

The use of diclofenac with concomitant 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. Additionally, this product should also not be combined with other analgesics containing paracetamol.

Caution is indicated in the elderly on basic medical grounds especially used in frail elderly patients or those with a low body weight.
Like other NSAIDs, diclofenac may mask the signs and symptoms of infection due to its pharmacodynamic properties.

Caution is advised in the administration of paracetamol to patients with moderate and severe renal insufficiency, mild to moderate hepatocellular insufficiency (including Gilbert's syndrome), severe hepatic insufficiency (Child-Pugh > 9), acute hepatitis, concomitant treatment with medicinal products affecting hepatic functions, glucose-6-phosphatedehydrogenase deficiency, haemolytic anaemia, dehydration, alcohol abuse and chronic malnutrition.

Gastrointestinal effects

Gastrointestinal bleeding or ulceration or perforation, which can be fatal, have 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. The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2 Posology and method of administration) When gastrointestinal bleeding or ulceration occur in patients receiving diclofenac, the medicinal product should be withdrawn

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, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see 4.3 Contra-indications) 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 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 (see below and section 4.5 Interactions with other medicinal products and other forms of interaction).

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the early stages of treatment. Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, anti-platelet agents such as aspirin 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 inpatients with ulcerative colitis or Crohn's disease), as their condition may be exacerbated (see section 4.8 Undesirable effects) .

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.

Cardiovascular and cerebrovascular effects

Appropriate monitoring and advice are required for patients with a history of hypertension and/or congestive heart failure (NYHA-1) as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that the use of diclofenac, particularly at high doses (150 mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).

Patients with congestive heart failure (NYHA-1) 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. 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.

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.

Hepatic effects

Close medical surveillance is required when prescribing Cataflam 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 etc), 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.

The risks of a paracetamol overdose are greater in those with non-cirrhotic alcoholic liver disease due to alcohol intake. Caution should be exercised in patients with chronic alcoholism. In such cases, the dose should not exceed 2 g daily. Alcohol should not be used during treatment with paracetamol.

Higher doses of paracetamol than recommended lead to a risk of very severe liver damage. Clinical signs of liver damage from paracetamol generally only start after a few days and climax after 4-6 days as a rule. An antidote should be administered as soon as possible. See also under 4.9 Overdose.

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 in 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 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 Cataflam (see section 4.8 Undesirable effects). Patients appear to be at highest risk of 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. Cataflam should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

As with other NSAIDs, allergic reactions, including anaphylactic or 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.

Haematological effects

Use of Cataflam is recommended only for short-term treatment. If, however, Cataflam is used for a prolonged period, monitoring of the blood count is recommended, as with other NSAIDs.
Like other NSAIDs, Cataflam may temporarily inhibit platelet aggregation. Patients with defects of haemostasis 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.

Sucrose

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions are those observed for both diclofenac and paracetamol.

Diclofenac:
CYP2C9 inhibitors: Caution is recommended when co-prescribing diclofenac with CYP2C9 inhibitors (such as voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac.

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.

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 precautions for use).

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.

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

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 risk of gastrointestinal ulceration or bleeding (see section 4.4 Special warnings and precautions for use).

Anticoagulants and anti-platelet agents: Caution is recommended since concomitant administration could increase the risk of gastrointestinal bleeding (see section 4.4 Special warnings and special precautions for

use). Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4.). There are also 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.

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.

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

Paracetamol:
Pharmacodynamic interactions
Warfarin: Studies have shown that the effect of warfarin may be enhanced in treatment with paracetamol. The effect appears to increase with the dose of paracetamol but can occur at doses of just 1.5-2.0 g paracetamol a day for at least 5-7 days. Single doses of paracetamol at normal dosage are not deemed to have any effect.

Pharmacokinetic interactions
Effects of other medicinal products on the pharmacokinetics of paracetamol:
Enzyme-inducing substances: In pharmacokinetic studies, enzyme-inducing medicinal products such as certain anti-epileptic drugs

(phenytoin, phenobarbital, carbamazepine) have been shown to reduce the plasma AUC of paracetamol to approx. 60%. Other substances with enzyme-inducing properties, e.g. rifampicin and St. John's wort (hypericum) are also suspected of producing lower concentrations of paracetamol. In addition, there may be a greater risk of liver damage from treatment with the maximum recommended dose of paracetamol in patients who are on enzyme-inducing medicinal products.

Probenecid: Probenecid immediately halves clearance of paracetamol by inhibiting its conjugation with glucuronic acid. This should mean that the dose of paracetamol can be halved in simultaneous treatment with probenecid.

Metaclopramide: The absorption rate of paracetamol may be increased by metoclopramide, but the substances can be given together. The absorption of paracetamol is reduced by cholestyramine. Cholestyramine should not be given within an hour if the maximum analgesic effect is to be achieved.

Zidovudine: May affect paracetamol metabolism and vice versa, which may add to the toxicity of both.

Chloramphenicol: Paracetamol can affect the pharmacokinetics of chloramphenicol. Analysis of plasma chloramphenicol is therefore recommended with combination therapy.

Effect on laboratory tests
Paracetamol may affect uric acid tests in serum through the phosphotungstic acid and blood sugar tests by glucose-oxidase-peroxidase.

4.6 Fertility, 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.

From the 20th week of pregnancy onward, diclofenac may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, 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. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to diclofenac for several days from gestational week 20 onward. Diclofenac should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

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

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above)

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, Dolipar is contraindicated during the third trimester of pregnancy.

Lactation
Both diclofenac and paracetamol pass into the breast milk in small amounts. Therefore, Dolipar should not be administered during breast feeding 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 Dolipar should be considered.

4.7 Effects on ability to drive and use machines.

Patients who experience dizziness, vertigo, somnolence or other central nervous system disturbances, including visual
disturbances, while taking NSAIDs should refrain from driving or using machines.

4.8 Undesirable effects

Adverse drug reactions from clinical trials and/or spontaneous or literature cases (Table 1) are listed by MedRA system order 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 using the following convention: (CIOMS III):
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 most commonly observed adverse events associated with diclofenac use are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4 Special warnings and precautions for use). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of coilitis and Crohn's disease (see section 4.4 Special warnings and precautions for use) have been reported following administration. Less frequently, gastritis has been observed. Paracetamol side effects are generally rare.

The following undesirable effects include those reported with diclofenac and paracetamol short-term or long-term use:

Blood and lymphatic system disorders
Rare: Platelet disorders, stem cell disorders, agranulocytosis, thrombocytopenia, neutropenia, leukopenia, haemolytic anaemia, pancytopenia
Very rare: Aplastic anaemia

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

Metabolism and nutrition disorders
Very rare: Hypoglycaemia

Psychiatric disorders
Rare: Depression, hallucination, confusion
Very rare: Disorientation, insomnia, nightmare, irritability, psychotic disorder.

Nervous system disorders:
Common: Headache, dizziness
Rare: Somnolence, tremor
Very rare: Paraesthesia, memory impairment, convulsion, anxiety, meningitis aseptic, dysgeusia, cerebrovascular accident.

Eye disorders
Very rare: Visual impairment, vision blurred, diplopia

Ear and labyrinth disorders
Common: Vertigo
Very rare: Tinnitus, impaired hearing

Cardiac disorders
Uncommon: Myocardial infarction, cardiac failure, palpitations, chest pain
Frequency not known: Kounis Syndrome

Vascular disorders
Very rare: Hypertension, vasculitis.

Respiratory, thoracic and mediastinal disorders
Rare: Asthma/bronchospasm (including dyspnea).
Very rare: Pneumonitis

Gastrointestinal disorders
Common: Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, decreased appetite
Rare: Gastritis, gastrointestinal hemorrhage, Hematemesis, diarrhea hemorrhagic, melena, gastrointestinal ulcer (with or without bleeding or perforation)
Very rare: Colitis (including hemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis
Not known: Ischemic colitis

Hepatobiliary disorders
Common: Increased transaminases
Rare: Hepatitis, jaundice, abnormal liver function
Very rare: Fulminant hepatitis, hepatic necrosis, hepatic failure

Skin and subcutaneous tissue disorders
Common: Rash
Rare: Urticaria, angioedema, allergic dermatitis
Very rare: Dermatitis bullous, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, alopecia, photosensitivity reaction, purpura, Henoch-Schonlein purpura, pruritus

Renal and urinary disorders
Very rare: Acute kidney injury (acute renal failure), hematuria, proteinuria, nephritic syndrome, tubulointerstitial nephritis, renal papillary necrosis, sterile pyuria (cloudy urine).

General disorders and administration site conditions
Rare: Oedema

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Pharmacy and Poison Board Pharmacovigilance Electronic Reporting System (PvERS) at https://pv.pharmacyboardkenya.org.

4.9 Overdose

At excess doses the conjugation capacity in the liver may be reduced after which a large part of the dose is metabolised by oxidation. If stores of glutathione are depleted the reactive intermediate metabolites bind irreversibly to liver macromolecules. Clinical symptoms of liver damage generally only appear after a few days. It is therefore crucial to start treatment with an antidote as soon as possible in order to prevent or minimise liver damage after toxic doses.

Toxicity:
See below under Treatment for information on toxic plasma concentrations. 5 g over 24 hours for up to 3½ year-olds, 15-20 g for adults, 10 g to an alcoholic produced lethal intoxication. A toxic dose for adults is generally 140 mg/kg and a toxic dose for children approx. 175 mg/kg. Starvation, dehydration, medication with enzyme-inducing agents (antiepileptic's, promethazine etc.) and chronic high alcohol consumption are risk factors and can cause pronounced liver damage even in small doses. Even sub-acute "therapeutic" overdose has led to serious intoxication with doses varying from 6 g/day for a week, 20 g for 2 or 3 days, etc.

Symptoms:
For a few hours following ingestion and for the first 1-2 days there may be abdominal pains, nausea and vomiting. After 2-3 days there may be signs of liver damage with elevated transaminase levels, falling prothrombin values, coagulopathy, icterus, malaise, hypoglycaemia, hypokaliemia, hypophosphataemia, metabolic acidosis, disseminated intravasal coagulation. Manifest liver failure and hepatic coma. Liver damage generally peaks after 4-6 days. Kidney damage may be secondary to liver damage or as the sole or main toxic manifestation within 24- 72 hours of the overdose. Pancreatitis and toxic myocardial damage with arrhythmia and heart failure have been reported. At

extremely high concentrations there have been reports of loss of consciousness combined with acidosis and hyperglycaemia. Pancytopaenia.

Treatment:
If necessary, gastric irrigation and activated charcoal.
Management of acute poisoning should consist of supportive measures and symptomatic treatment, including managing complications such as hypotension, renal failure, convulsions, GI disorders and respiratory depression.

Plasma paracetamol concentration should be measured at 4 hours or later after ingestion. Acute response. False lows may be measured if acetylcysteine has already been administered. If an antidiarrhoeal has been taken a new sample should be taken 2 hours after the first (delayed peak concentration). Treatment with acetylcysteine initiated within 8-10 hours provides complete protection from liver damage, after which the effect diminishes. Acetylcysteine is used if the paracetamol concentration is above the following levels at respective points: 1000 micromol/l at 4 hours, 700 micromol/l at 6 hours and 450 micromol/l at 9 hours after exposure. In cases of concomitant alcoholism, starvation, dehydration, impaired liver function or medication with enzyme-inducing drugs there may be grounds for setting the threshold for antidote therapy at about ¾ the listed levels. The method of administration is adapted to the circumstances (level of consciousness, tendency to vomiting etc.). However, intravenously administered acetylcysteine is deemed more effective and safer.

Dosage of acetylcysteine: Intravenously initially 150 mg/kg in 200-300 ml isotonic infusion solution over 15 minutes, then 50 mg/kg in 500 ml 50 mg/ml glucose over 4 hours and then 6.25 mg/kg/hour over 16 hours (75 mg/kg dissolved in 500 ml isotonic glucose solution and administered over 12 hours). Fluid volumes can be reduced, if necessary. Contact the National (local) Poisons Information Centre for information.) for a specific schedule. (In exceptional circumstances, acetylcysteine may be administered orally if the intravenous route is not available. Contact the National (local) Poisons Information Centre for information. Acetylcysteine may provide some protection even after 10 hours, but in such cases prolonged treatment should be administered. Acetylcysteine also reduces mortality in the event of manifest paracetamol-induced liver failure (please discuss with the Poisons Information Centre). Close monitoring of hepatic and renal function, coagulation status, fluid and electrolyte status. Liver and kidney failure therapy is often required in cases where the deadline for effective antidote treatment has passed and there are toxic concentrations present. Haemoperfusion may be indicated in special circumstances. In extreme cases a liver transplant may be required.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Diclofenac

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

Mechanism of action

Diclofenac sodium is 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 of 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 sodium elicit a clinical response characterised 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 sodium rapidly relieves both spontaneous pain and pain on movement and reduces inflammatory swelling and wound oedema.

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.

There is limited clinical trial experience of the use of diclofenac in Juvenile Rheumatoid Arthritis (JRA)/Juvenile Idiopathic Arthritis (JIA) paediatric patients. In a randomized, double-blind, 2-week, parallel group study in children aged 3-15 years with JRA/JIA, the efficacy and safety of daily 2-3 mg/kg BW diclofenac was compared with acetylsalicylic acid (ASS, 50-100 mg/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 randomized, double-blind, 6-week, parallel group study in children aged 4-15 years with JRA/JIA,

the efficacy of diclofenac (daily dose 2-3 mg/kg BW, n=22) was comparable with that of indomethacin (daily dose 2-3mg/kg BW, n=23).

Paracetamol
Pharmacotherapeutic group: Analgesic, antipyretic, ATC code: N02BE01

Paracetamol is an aniline derivative with analgesic and antipyretic actions similar to those of acetylsalicylic acid but paracetamol does not cause gastrointestinal irritation and is also well tolerated by patients with ulcers. Paracetamol does not affect thrombocyte aggregation or bleeding time. Paracetamol is generally well tolerated by patients who are hypersensitive to acetylsalicylic acid.

The antipyretic effect is achieved through action on the hypothalamic heat-regulation centre, whereby heat dissipation is increased.

The latency period for the analgesic effect is approx. 1⁄2 hour. The peak effect is achieved within 1-2 hours and lasts for 4-5 hours. The course of the antipyretic effect is somewhat slower. Thus the latency period is approx. 1⁄2-1 hour, maximum reduction in fever is recorded after 2-3 hours and the effect lasts for about 8 hours.

5.2 Pharmacokinetic properties

Diclofenac

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 micromol/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 metabolized 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.

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

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

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

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 (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:

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:

Total systemic clearance of diclofenac in plasma is 263 ± 56mL/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 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.

Special Populations

Elderly: No relevant age-dependent differences in the drug's absorption, metabolism, or excretion have been observed, other than the finding that in five elderly patients, a 15 minute iv infusion resulted in 50%

higher plasma concentrations than expected with young healthy subjects.

Patients with 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 <10ml/min, the calculated steady-state plasma levels of hydroxy metabolites are about 4 times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile.

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

Paracetamol

Absorption

Paracetamol is absorbed well when administered orally. Peak plasma concentration of paracetamol is achieved within 1⁄2-1 hour.

Distribution

Paracetamol is distributed rapidly into all tissues. Blood, plasma and saliva concentrations are comparable. Protien binding is low with recommended doses.

Biotransformation

The plasma half-life is approx. 2 hours. Paracetamol is primarily metabolised in the liver by conjugation to glucuronide and sulphate. A small amount (about 3-10% of a therapeutic dose) is metabolised by oxidation by cytochrome P450 and the reactive intermediate metabolite thus formed is bound preferentially to the liver glutathione and excreted as cysteine and mercapturic acid conjugates.

Elimination

Excretion occurs via the kidneys. Approx. 2-3% of a therapeutic dose is excreted unchanged, approx. 80-90% as glucuronide and sulphate and a smaller amount as cysteine and mercapturic acid derivatives.

Renal insufficiency

In patients with severe renal insufficiency (creatinine clearance < 10 ml/min), elimination of paracetamol and its metabolites is delayed.

Elderly patients

Conjugation is unchanged in this patient group.

Paediatric population

In neonates and children < 12 years sulphate conjugation is the main elimination route and glucuronidation is lower than in adults. Total elimination in children is comparable to that in adults, due to an increased capacity for sulphate conjugation. In children the formation of the toxic intermediate product is reduced compared with adults. Additionally, neonates have an increased ability to replete liver glutathione. Therefore, severe liver damage caused by paracetamol would seem to be rarer in children than in adults. The elimination half-life of paracetamol is 2–2.5 hours in children.

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 foetal 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 foetal 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 lactation).

6. Pharmaceutical particulars

6.1 List of excipients

Maize Starch
Dicalcium Phosphate
Povidone K-30
Polyethylene Glycol 6000
Sorbitol Solution 70%
Sodium Methylparaben
Sodium Propylparaben

Purified Talc
Magnesium Stearate
Colloidal Silicon Dioxide
Opadry white

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage:
Store below 30℃
Protect from light.
Keep all medicines out of reach of children.

6.5 Nature and contents of container
10 tablets in Alu/PVC blister in packs of 100.
1 x 10 tablets x 10 blister strips.

6.6 Special precautions for disposal and other handling:
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder and Manufacturing site address:
Dinlas Pharma EPZ Limited.
P.O Box 22661-00505,
Nairobi, Kenya.
Telephone: +254 782500800, 782500700
E-Mail: info@dinlaspharma.com

8. Marketing authorization number
CTD8767.

9. Date of first registration
03-03-2024.

10. Date of revision of the text:
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