CIPZEN D Tablets (Diclofenac sodium + Serratiopeptidase)

Black Box Warning

Cardiovascular Risk
NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. Diclofenac sodium tablets are contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.
Gastrointestinal Risk
NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events, including inflammation, bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious GI events.

Qualitative and Quantitative Composition

Each Film coated tablet contains

Diclofenac Sodium I.P.50mg

Serratiopeptidase I.P. 10mg

(Eq.20000 Serratiopeptidase Units)

Excipients .....Q.S

Approved Colour used in tablets

Dosage form and Strength

Diclofenac 50mg and Serratiopeptidase 10mg Oral tablet

Clinical Particulars

Therapeutic Indications

For the treatment of acute pain in adults.

Posology and Method of Administration

Posology

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.

Adults: 75 mg to 150 mg daily in two or three divided doses.

The recommended maximum daily dose of diclofenac sodium is 150 mg.

Use in Special Populations

Geriatric Patients

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 particular caution in such patients who generally are more prone to adverse reactions. In particular, it is recommended that the lowest effective dosage be used in frail elderly patients or those with a low body weight and the patient should be monitored for GI bleeding during NSAID therapy.

Patients with Renal Impairment

Diclofenac sodium 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 sodium to patients with mild to moderate renal impairment.

Patients with Hepatic Impairment

Diclofenac sodium is contraindicated in patients with severe hepatic impairment. 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 sodium to patients with mild-to-moderate hepatic impairment.

Paediatric Patients

Diclofenac sodium 50 mg tablets are not suitable for use in children.

Method of Administration

For oral administration.

To be taken whole with a glass of water or any other liquid, preferably with or after food.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Active, or gastric or intestinal ulcer, bleeding or perforation.
- History of GI 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), ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- Like other NSAIDs, diclofenac sodium is also contraindicated in patients in whom attacks of asthma, angio-oedema, urticaria or acute rhinitis are precipitated by ibuprofen, acetylsalicylic acid or other NSAIDs.

Special Warnings and Precautions for Use

General

Undesirable effects may be minimised 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. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight.

As with other NSAIDs, including diclofenac sodium, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur 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 sodium.

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

This medicine contains lactose and, therefore, is not recommended for patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.

GI Effects

GI bleeding (haematemesis, melaena), ulceration or perforation, which can be fatal, has been reported with all NSAIDs, including diclofenac sodium, and may occur at any time during treatment, with or without warning symptoms or a previous history of serious GI events. They generally have more serious consequences in the elderly. If GI bleeding or ulceration occurs in patients receiving diclofenac sodium, the medicinal product should be withdrawn.

As with all NSAIDs, including diclofenac sodium, close medical surveillance is imperative and particular caution should be exercised when prescribing diclofenac sodium in patients with symptoms indicative of GI disorders or with a 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 sodium, and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation.

The elderly have an increased frequency of adverse reactions to NSAIDs, especially GI 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. 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 GI 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 that 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.

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

Patients with Hepatic Impairment

Close medical surveillance is required when prescribing diclofenac sodium to patients with impairment of hepatic function, as their condition may be exacerbated.

As with other NSAIDs, including diclofenac sodium, values of one or more liver enzymes may increase. During prolonged treatment with diclofenac sodium, 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 sodium should be discontinued.

Hepatitis may occur with diclofenac sodium without prodromal symptoms.

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

Patients with Renal Impairment

As fluid retention and oedema have been reported in association with NSAID therapy, including diclofenac sodium, 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 sodium 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 diclofenac sodium. 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 tablets 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 sodium after careful consideration. As the cardiovascular risks of diclofenac sodium may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The pateint'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 sodium.

Clinical trial and epidemiological data consistently point towards increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke) associated with the use of diclofenac sodium, particularly at high dose (150 mg 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 sodium after careful consideration.

Haematological Effects

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

Diclofenac sodium 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.

Female Fertility

The use of diclofenac sodium may impair female fertility and is not recommended in women attempting to conceive. In women who may have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of diclofenac sodium should be considered.

Drug Interactions

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

Lithium

If used concomitantly, diclofenac sodium may raise plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.

Digoxin

If used concomitantly, diclofenac sodium 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 sodium 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 sodium affects the action of anticoagulants, there are reports of an increased risk of haemorrhage in patients receiving diclofenac sodium 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 NSAIDs, diclofenac sodium in high doses can reversibly inhibit platelet aggregation.

Other NSAIDS, including cyclo-oxygenase-2selective inhibitors and corticosteroids

Co-administration of diclofenac sodium and other systemic NSAIDs or corticosteroids may increase the risk of GI bleeding or ulceration. Avoid concomitant use of two or more NSAIDs.

SSRIs

Concomitant administration of SSRIs may increase the risk of GI bleeding.

Antidiabetics

Clinical studies have shown that diclofenac sodium 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 sodium. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

Methotrexate

Diclofenac sodium can inhibit the tubular renal clearance of methotrexate hereby increasing methotrexate levels. Caution is recommended when NSAIDs, including diclofenac sodium, 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 sodium, are given within 24 hours of each other. This interaction is mediated through accumulation of methotrexate resulting from the impairment of renal excretion in the presence of the NSAID.

Ciclosporin

Diclofenac sodium, 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

There is 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 sodium, 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 sodium. Therefore, it is recommended to administer diclofenac sodium 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 to 12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Potent CYP2C9 Inhibitors

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

Use in Special Populations

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 sodium 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 the following:

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

Consequently, diclofenac sodium tablets are contraindicated during the third trimester of pregnancy.

Lactating Women

Like other NSAIDs, diclofenac sodium passes into the breast milk in small amounts. Therefore,

diclofenac sodium should not be administered during breastfeeding in order to avoid undesirable effects in the infant.

Female Fertility

As with other NSAIDs, the use of diclofenac sodium 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 sodium should be considered.

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.

Undesirable Effects

Diclofenac Sodium

Adverse reactions (Table 1) are ranked under the heading of frequency, with the most frequent first, using 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); and, not known: cannot be estimated from the available data.

The following undesirable effects include those reported with either short-term or long-term use.

Table 1

Blood and lymphatic system disorders	
Very rare	Thrombocytopaenia, leucopaenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis
Immune system disorders	
Rare Very rare	Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock) Angioneurotic oedema (including face oedema)
Psychiatric disorders	
Very rare	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder
Nervous system disorders	
Common Rare Very rare Unknown	Headache, dizziness Somnolence, tiredness Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident Confusion, hallucinations, disturbances of sensation, malaise
Eye disorders	
Very rare Unknown	Visual disturbance, vision blurred, diplopia Optic neuritis
Ear and labyrinth disorders	
Common Very rare	Vertigo Tinnitus, hearing impaired
Cardiac disorders	

Uncommon*	Myocardial infarction, cardiac failure, palpitations, chest pain
Unknown	Kounis syndrome
Vascular disorders	
Very rare	Hypertension, hypotension, vasculitis
Respiratory, thoracic and mediastinal disorders	
Rare Very rare	Asthma (including dyspnoea) Pneumonitis
GI disorders	
Common Rare Very rare Unknown	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain Flatulence, anorexia Gastritis, GI haemorrhage, haematemesis Diarrhoea (haemorrhagic), melaena, GI 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	
Common Rare Very rare	Transaminases increased Hepatitis, jaundice, liver disorder Fulminant hepatitis, hepatic necrosis, hepatic failure
Skin and subcutaneous tissue disorders	
Common Rare Very rare	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	
Very rare	Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis
Reproductive system and breast disorders	
Very rare	Impotence
General disorders and administration site conditions	
Rare	Oedema

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

Clinical trial and epidemiological data consistently point towards an increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke) associated with the use of diclofenac sodium, particularly at high dose (150 mg daily) and in long-term treatment.

Nicolau’s syndrome, also known as livedo-like dermatitis or embolia cutis medicamentosa, is a rare complication reported following intramuscular diclofenac sodium injection.

Serratiopeptidase was well tolerated in short-term clinical trials, but long-term safety has not been evaluated. Rare, serious adverse effects reported with serratiopeptidase include eosinophilic

pneumonitis, bullous pemphigoid, haemorrhage in a patient with Behcet disease and, possibly, Stevens-Johnson syndrome.

Reporting of suspected adverse reactions

If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the National Pharmacovigilance Programme of India (PvPI) by calling on 1800 267 7779 (Cipla number) or you can report to PvPI on 1800 180 3024. By reporting side effects, you can help provide more information on the safety of this product.

Overdose

Symptoms

There is no typical clinical picture resulting from diclofenac sodium overdosage. Overdosage can cause symptoms such as headache, nausea, vomiting, epigastric pain, GI haemorrhage, diarrhoea, dizziness, disorientation, excitation, coma, drowsiness, tinnitus, fainting or convulsions. In the case of significant poisoning, acute renal failure and liver damage are possible.

Therapeutic Measures

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

Special measures such as forced diuresis, dialysis or haemo-perfusion are probably of no help in eliminating NSAIDs, including diclofenac sodium, 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.

Pharmacological Properties

Mechanism of Action

Diclofenac Sodium

Diclofenac sodiumis a NSAID 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.

Serratiopeptidase

Serratiopeptidase is also a potent anti-inflammatory agent that exerts fibrinolytic and anti-oedematic actions. The therapeutic enzyme reduces inflammation and swelling in the affected area.

Pharmacodynamic Properties

Pharmacotherapeutic group: NSAlDs.

Serratiopeptidase is a bacterial, peptide-cleaving enzyme obtained from *Serratia marcescens*.

Pharmacokinetic Properties

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 concentration of diclofenac sodium is reached at about 2 hours (50 mg dose produces 1,511± 466 ng/ml).

About half of the administered diclofenac sodium 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.

The active substance is 99.7% protein-bound, mainly to albumin (99.4%).

Diclofenac sodium enters the synovial fluid, where maximum concentrations are measured 2 to 4 hours after the peak plasma values have been attained. The apparent half-life for elimination from the synovial fluid is 3 to 6 hours. At 2 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 sodium 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 of diclofenac sodium 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 sodium.

The total systemic clearance of diclofenac sodium in plasma is 263 ± 56 mL/min (mean value ± 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.

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.

Characteristics in Patients

Geriatric Patients: No relevant age-dependent differences in the drug's absorption, metabolism or excretion have been observed, other than the finding that in 5 elderly patients, a 15 minute intravenous (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 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.

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

Non-Clinical Properties

Animal Toxicology or Pharmacology

Not applicable.

Description

Diclofenac sodium is a benzene-acetic acid derivative, designated chemically as 2-[(2,--dichlorophenyl) amino] benzeneacetic acid, monosodium salt.

Serratiopeptidase is an extracellular proteolytic enzyme produced by *Serratia marcescens* ATCC 27117 (formerly *Serratia* strain E-15. composed of 470 amino acids, with a molecular weight of approximately 50,000 kilodaltons. The active site of the enzyme, which contains a zinc atom, hydrolyses nonterminal peptide linkages of polypeptides. Maximal proteolytic activity occurs at 40°C (104°F) and at a pH of approximately 8 (range, 6 to 10). Maintaining the temperature at 55°C (131°F) for 15 minutes inactivates the enzyme.

Pharmaceutical Particulars

Packaging information

Each Strip contains 10 tablets

Storage and Handling Instructions

Store in a cool dry place. Keep out of reach of children

Patient Counselling Information

● What is CIPZEN D Tablets and what are they used for?

CIPZEN D Tablets are a combination of two medicines: Diclofenac sodium and serratiopeptidase. Diclofenac sodium is a non-steroidal anti-inflammatory drug (NSAID) that works by blocking the release of certain chemical messengers in the brain that cause pain and inflammation (redness and swelling). Serratiopeptidase is an enzyme that works by breaking down abnormal proteins at the site of inflammation and promotes healing.

Diclofenac sodium plus serratiopeptidase is used for pain relief.

● Do not take if you have an allergy to this drug

Do not take this medicine if

- you are allergic to diclofenac sodium, aspirin, ibuprofen or any other NSAID, or to any of the other ingredients of this medicine.

Signs of a hypersensitivity reaction include swelling of the face and mouth (angio-oedema), breathing problems, chest pain, runny nose, skin rash or any other allergic type reaction.

● Before you take CIPZEN D Tablets, tell your HCP about other medication

Some medicines can interfere with your treatment. Please tell your doctor or pharmacist if you are taking any of the following:

- Medicines to treat diabetes
- Anticoagulants (blood-thinning tablets such as warfarin)
- Diuretics (water tablets)
- Lithium (used to treat some mental problems)
- Methotrexate (for treatment of some inflammatory diseases and some cancers)
- Ciclosporin and tacrolimus (used to treat some inflammatory diseases and after transplants)
- Trimethoprim (a medicine used to prevent or treat urinary tract infections)
- Quinolone antibiotics (for infections)
- Any other NSAID or COX-2 (cyclo-oxygenase-2) inhibitor, e.g. aspirin or ibuprofen
- Mifepristone (a medicine used to terminate pregnancy)
- Cardiac glycosides (e.g. digoxin), used to treat heart problems
- Medicines known as SSRIs (used to treat depression)
- Oral steroids (an anti-inflammatory drug)
- Medicines used to treat heart conditions or high blood pressure, e.g. beta-blockers or ACE inhibitors
- Voriconazole (a medicine used to treat fungal infections).
- Phenytoin (a medicine used to treat seizures)
- Colestipol/cholestyramine (used to lower cholesterol)

Always tell your doctor or pharmacist about all the medicines you are taking. This means medicines you have bought yourself as well as medicines on prescription from your doctor.

● How should I take CIPZEN D Tablets?

The doctor will tell you how many **CIPZEN D Tablets** 50 mg tablets to take and when to take them. Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Take the tablets with or after food. Swallow the tablets whole with a glass of water or any other liquid.

DO NOT crush or chew the tablets.

The recommended dose is as below:

Adults: 75 to 150 mg daily in two or three divided doses. The number of tablets which you take will depend on the strength the doctor has given you.

Elderly: The lowest effective dose should be used. Your doctor may advise you to take a dose that is lower than the usual adult dose if you are elderly. Your doctor may also want to check closely that the diclofenac sodium tablets are not affecting your stomach.

Children: These tablets are not suitable for children below 12 years of age.

The doctor may also prescribe another drug to protect the stomach to be taken at the same time, particularly if you have had stomach problems before, or if you are elderly, or taking certain other drugs as well.

If you take more CIPZEN D Tablets 50 mg than you should:

If you, or anyone else, accidentally take too much this medicine, tell your doctor or go to your nearest hospital casualty department immediately. Take your medicine pack with you so that the doctor can see what you have taken.

Symptoms of an overdose can include headache, nausea (feeling sick), vomiting, abdominal pain, stomach or intestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, ringing in the ears, fainting, or occasionally convulsions (seizures, uncontrolled fits).

If you forget to take CIPZEN D Tablets 50 mg

It is important that you do not miss a dose. If you forget to take a dose, take one as soon as you remember. If it is nearly time for your next dose, just take the next dose and forget about the one you missed. Do NOT take a double dose to make up for a forgotten tablet. Do not take more than 150 mg in 24 hours. If you have trouble remembering to take the tablets, tell your doctor or pharmacist.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

● What are the possible side effects?

Like all medicines, diclofenac sodium can cause side effects, although not everybody gets them.

Some side effects can be serious

STOP TAKING CIPZEN D Tablets and tell your doctor straight away if you notice the following:

- Stomach pain, indigestion, heartburn, wind, nausea (feeling sick) or vomiting (being sick)
- Any sign of bleeding in the stomach or intestine, e.g. when emptying your bowels, blood in vomit or black, tarry faeces
- Allergic reactions, which can include skin rash, itching, bruising, painful red areas, peeling or blistering
- Wheezing or shortness of breath (bronchospasm)
- Swollen face, lips, hands or fingers
- Yellowing of your skin or the whites of your eyes
- Persistent sore throat or high temperature
- An unexpected change in the amount of urine produced and/or its appearance.
- Mild cramping and tenderness of the abdomen, starting shortly after the start of the treatment with diclofenac sodium and followed by rectal bleeding or bloody diarrhea usually within 24 hours of the onset of abdominal pain.
- Stevens-Johnson syndrome (serious illness with blistering of the skin, mouth, eyes and genitals)

If you notice that you are bruising more easily than usual or have frequent sore throats or infections, tell your doctor.

Tell your doctor immediately if you notice the following:

- Chest pain, which can be a sign of a potentially serious allergic reaction called Kounis syndrome

The side effects listed below have also been reported.

Common *(may affect up to 1 in 10 people)*

- Stomach pain, heartburn, nausea, vomiting, diarrhoea, indigestion, wind, loss of appetite
- Headache, dizziness, vertigo
- Skin rash or spots
- Raised levels of liver enzymes in the blood

Rare *(may affect up to 1 in 1,000 people)*

- Stomach ulcers or bleeding (there have been very rare reported cases resulting in death, particularly in the elderly)
- Gastritis (inflammation, irritation or swelling of the stomach lining)
- Vomiting blood
- Diarrhoea with blood in it or bleeding from the back passage
- Black, tarry faeces or stools
- Drowsiness, tiredness
- Hypotension (low blood pressure, symptoms of which may include faintness, giddiness or light headedness)
- Skin rash and itching
- Fluid retention, symptoms of which include swollen ankles
- Liver function disorders, including hepatitis and jaundice

Very rare *(may affect up to 1 in 10,000 people)*

Effects on the nervous system

Tingling or numbness in the fingers, tremor, blurred or double vision, hearing loss or impairment, tinnitus (ringing in the ears), sleeplessness, nightmares, mood changes, depression, anxiety, mental disorders, disorientation and loss of memory, fits, headaches together with a dislike of bright lights, fever and a stiff neck, disturbances in sensation.

Effects on the stomach and digestive system

Constipation, inflammation of the tongue, mouth ulcers, inflammation of the inside of the mouth or lips, taste changes, lower gut disorders (including of the colon or worsening of ulcerative colitis or Crohn’s disease).

Effects on the heart, chest or blood

Palpitations (fast or irregular heart beat), chest pain, hypertension (high blood pressure), inflammation of blood vessels (vasculitis), inflammation of the lung (pneumonitis), heart disorders, including congestive heart failure or heart attack, blood disorders (including anaemia).

Effects on the liver or kidneys

Kidney or severe liver disorders including liver failure, presence of blood or protein in the urine.

Effects on skin or hair

Serious skin rashes, including Stevens-Johnson syndrome, Lyell's syndrome and other skin rashes which may be made worse by exposure to sunlight; hair loss.

Other side effects that have also been reported include the following:

Inflammation of the pancreas, impotence.

Facial swelling, inflammation of the lining of the brain (meningitis), stroke, throat disorders, confusion, Nicolau syndrome, hallucinations, malaise (general feeling of discomfort), inflammation of the nerves in the eye.

Do not be alarmed by this list – most people take tablets containing diclofenac sodium without any problems.

If any of the side effects becomes serious, or if you notice side effects not listed in this leaflet, please tell your doctor. He/she may want to give you a different medicine.

Reporting of suspected adverse reactions

If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the National Pharmacovigilance Programme of India (PvPI) by calling on 1800 267 7779 (Cipla number) or you can report to PvPI on 1800 180 3024. By reporting side effects, you can help provide more information on the safety of this product.

● How should I store CIPZEN D Tablets?

Keep out of the sight and reach of children.

Do not use these tablets after the expiry date (which is printed after 'EXP:' on the carton).

Do not store above 25°C. Keep the tablets in their original pack.

Medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

● General information about the safe and effective use of this drug

Do not take CIPZEN D Tablets 50 mg in case of the following:

- You have now, or have ever had, a stomach(gastric) or duodenal (peptic) ulcer, or bleeding in the digestive tract (this can include blood in vomit, bleeding when emptying bowels, fresh blood in faeces or black, tarry faeces).
- You have had stomach or bowel problems after you have taken other NSAIDs.
- You have severe heart, kidney or liver failure.
- You have established heart disease and/or cerebrovascular disease, e.g. if you have had a heart attack, stroke, mini-stroke (TIA) or blockages to blood vessels to the heart or brain or an operation to clear or bypass blockages.
- You have or have had problems with your blood circulation (peripheral arterial disease).
- You are more than 6 months pregnant.

Warnings and precautions

Talk to your doctor or pharmacist before taking CIPZEN D Tablets in case of any of the

following:

- You suffer from any stomach or bowel disorders, including ulcerative colitis or Crohn’s disease.
- You have kidney or liver problems, or you are elderly.
- You have a condition called porphyria.
- You suffer from any blood or bleeding disorder. If you do, your doctor may ask you to go for regular check-ups while you are taking these tablets.
- You ever had asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (nasal polyps), chronic pulmonary diseases or infections of the respiratory tract.
- You are breastfeeding.
- You have angina, blood clots, high blood pressure, raised cholesterol or raised triglycerides.
- You have heart problems or if you had a stroke or you think you might be at risk of these conditions (e.g. if you have high blood pressure, diabetes or high cholesterol or are a smoker).
- You have diabetes.
- You smoke.
- You have systemic lupus erythematosus ([SLE] – an inflammatory, auto-immune disorder that causes symptoms such as joint pain, joint inflammation, skin rashes, fever), or any similar condition.
- You have an intolerance to some sugars such as lactose (these tablets contain lactose).
- Tell your doctor if you recently had or you are going to have a surgery of the stomach or intestinal tract before taking diclofenac sodium 50 mg, as diclofenac sodium can sometimes worsen wound healing in your gut after surgery.

Tell your doctor or pharmacist if you have any of these conditions because diclofenac sodium 50 mg might not be the right medicine for you.

Children

These tablets are not suitable for children below 12 years of age.

Diclofenac sodium 50 mg with food and drink

Take this medicine with or after food. Take the table whole with a glass of water or any other liquid.

Pregnancy and breastfeeding

Although not common, abnormalities have been reported in babies whose mothers have taken NSAIDs during pregnancy. You should not take diclofenac sodium 50 mg tablets during the last 3 months of pregnancy as it may affect the baby's circulation.

- You should advise your doctor or pharmacist if you think you might be pregnant or are up to 6 months pregnant.
- Taking diclofenac sodium 50 mg tablets may make it more difficult to become pregnant. You should talk to your doctor if you are planning to become pregnant, or if you have problems getting pregnant.
- You should avoid taking diclofenac sodium whilst breastfeeding.

Driving and using machines

Very occasionally people have reported that diclofenac sodium tablets have made them feel dizzy, tired or sleepy. Problems with eyesight have also been reported. If you are affected in this way, you should not drive or operate machinery.

Other special warnings

- You should take the lowest effective dose of diclofenac sodium for the shortest possible time particularly if you are underweight or elderly.
- There is a small increased risk of heart attack or stroke when you are taking any medicine like diclofenac sodium. The risk is higher if you are taking high doses for a long time. Always follow the doctor’s instructions on how much to take and how long to take it for.
- Whilst you are taking these medicines, your doctor may want to give you a check-up from time to time.
- If you have a history of stomach problems when you are taking NSAIDs, particularly if you are elderly, you must tell your doctor straightaway if you notice any unusual symptoms.
- Because it is an anti-inflammatory medicine, diclofenac sodium tablets may reduce the symptoms of infection, e.g. headache, and high temperature. If you feel unwell and need to see a doctor, remember to tell him or her that you are taking diclofenac sodium tablets.

Details of the Manufacturer

Mfd. By Cipla Ltd.

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Details of Permission or Licence Number with Date

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