For the use of only a Registered Medical Practitioner or a Hospital or a Laboratory

Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Aceclofenac, Paracetamol And Serratiopeptidase Tablets
(Brand Name: DOLOSTAT®-SP TABLETS)

Paracetamol: Box Warning About Its Liver Toxicity

Taking more than daily dose may cause serious liver damage or allergic reactions (e.g., swelling of the face, mouth and throat, difficulty in breathing, itching or rash). The risk of liver injury primarily occurs when patient take multiple products containing paracetamol/acetaminophen at one time and exceed the current maximum dose of 4,000 mg within a 24-hour period.

2. Qualitative and Quantitative Composition

Each film-coated tablet contains:
Aceclofenac IP ……. 100 mg.
Paracetamol IP ……..… 325 mg.
Serratiopeptidase IP ……. 15 mg.
(as enteric coated granules equivalent to enzyme activity 30,000 Units)
Excipients …… q.s.
Colours: Lake of Sunset Yellow FCF and Titanium Dioxide IP.

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Aceclofenac 100 mg, paracetamol 325 mg, and serratiopeptidase 15 mg (as enteric coated granules) per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

DOLOSTAT-SP Tablets are indicated for reducing swelling and inflammation associated with surgery, trauma, infection, and other painful inflammatory conditions.

4.2Posology and Method of Administration

For oral administration.
Adults: 1 tablet to be administered twice daily.

DOLOSTAT-SP Tablets should be administered preferably 2 hours after a meal. The tablet should be swallowed whole with water and strictly not to be cut, crushed or chewed.

- The maximum recommended dose of aceclofenac is 200 mg daily in divided doses.
- The maximum recommended dose of paracetamol is 4 g daily in divided doses.
- The maximum dose of serratiopeptidase is 60 mg/day in divided doses.

Or, as prescribed by the physician.

4.3Contraindications

DOLOSTAT-SP Tablets are contraindicated in the following:

- Known hypersensitivity to aceclofenac or to paracetamol or to serratiopeptidase or to any component of the formulation.
- Active or history of recurrent peptic ulcer, bleeding or bleeding disorders.
- History of GI bleeding or perforation, relating to previous NSAID therapy.
- Severe heart failure, hepatic failure and renal failure.
- Patients with established congestive heart failure (NYHA class II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- During the last trimester of pregnancy.
- Patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by aspirin or other NSAIDs.
- Acute porphyria.

4.4Special Warnings and Precautions for Use

Aceclofenac

Gastrointestinal (GI) Bleeding, Ulceration and Perforation: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events. The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID dose, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g., misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase GI risk.

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding), particularly in the initial stages of treatment. Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin. When GI bleeding or ulceration occurs in patients receiving aceclofenac, the treatment should be withdrawn. NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn’s disease) as their condition may be exacerbated.

Hypersensitivity Reactions: As with other NSAIDs, allergic reactions (including anaphylactic reactions), can occur without earlier exposure to the drug.

Dermatological: 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. 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. Aceclofenac should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Respiratory: Use with caution in patients suffering from or with a previous history of bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients.

Hematological: Aceclofenac may reversibly inhibit platelet aggregation. Patients with defect of hemostasis, bleeding diathesis or hematological abnormalities should be carefully monitored.

Hepatic: Close medical surveillance is also imperative in patients suffering from severe impairment of hepatic function. If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), aceclofenac should be discontinued. Hepatitis may occur without prodromal symptoms. Use of aceclofenac in patients with hepatic porphyria may trigger an attack.

Renal: Patients with mild renal or cardiac impairment and the elderly should be kept under surveillance, since the use of NSAIDs may result in deterioration of renal function. The lowest effective dose should be used and renal function monitored regularly. The importance of prostaglandins in maintaining renal blood flow should be taken into account in patients with impaired cardiac or renal function, those being treated with diuretics or recovering from major surgery. Effects on renal function are usually reversible on withdrawal of aceclofenac.

Cardiovascular: Caution is required in patients with a history of hypertension and/or heart failure, as fluid retention and edema have been reported in association with NSAID therapy. 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 edema have been reported in association with NSAID therapy. Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (e.g., myocardial infarction or stroke). There are insufficient data to exclude such a risk for aceclofenac.

Patients with uncontrolled hypertension, congestive heart failure, established ischemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with aceclofenac after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g., hypertension, hyperlipidaemia, diabetes mellitus, and smoking).

Fertility: The use of aceclofenac 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 aceclofenac should be considered.

Other NSAIDs (Including COX-2 Selective Inhibitors): The use of aceclofenac with concomitant aspirin/NSAIDs including cyclooxygenase-2 (COX-2) selective inhibitors should be avoided as this may increase the risk of adverse effects including the risk of GI bleeding.
Long Term Treatment: Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms. As a precautionary measure, all patients who are receiving NSAIDs for longer time should be regularly monitored for renal failure, hepatic function and blood counts.

Paracetamol
Hepatotoxicity: Significant overdose of paracetamol can lead to hepatotoxicity in some patients. Thus, do not exceed the recommended dose. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.
Other Paracetamol-Containing Products: Do not take with any other paracetamol-containing products, so as to avoid the chances of overdose.
Renal and Hepatic Impairment: Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment.
Alcohol: Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive paracetamol use, although rarely.

Serratiopeptidase
Blood Coagulation Disorders: Serratiopeptidase may interfere with blood clotting. Thus, serratiopeptidase should be used with caution in patients with blood coagulation disorders or under treatment with anticoagulants.
Surgery: Serratiopeptidase might increase bleeding during and after surgery. Thus, serratiopeptidase should be discontinued at least 2 weeks before a scheduled surgery.
Renal and Hepatic Impairment: Serratiopeptidase should be used with caution in patients with severe hepatic and renal disturbances.

4.5Drug Interactions
Aceclofenac
Lithium: Aceclofenac, like many NSAIDs, may increase plasma concentration of lithium and thus, increases risk of its toxicity.
Cardiac Glycosides (Digoxin): Through their renal effects, NSAIDs may increase plasma glycoside levels, exacerbate cardiac failure and reduce the glomerular filtration rate (GFR) in patients receiving glycosides.
Diuretics: Aceclofenac, like other NSAIDs, may inhibit the activity of diuretics. Although it was not shown to affect blood pressure control when co-administered with bendrofluazide, interactions with other diuretics cannot be ruled out. When concomitant administration with potassium-sparing diuretics is employed, serum potassium should be monitored. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Anticoagulants: Like other NSAIDs, aceclofenac may enhance the activity of anticoagulants such as warfarin. Close monitoring of patients on combined anticoagulant and aceclofenac therapy should be undertaken.

Antihypertensive Drugs: NSAIDs may reduce the effect of antihypertensives. The risk of acute renal insufficiency, which is usually reversible, may be increased in some patients with compromised renal function (e.g., dehydrated patients or elderly patients) when angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists are combined with NSAIDs. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Antidiabetic Agents: 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 hypoglycemic and hyperglycemic effects. Thus, with aceclofenac, consideration should be given to adjustment of the dosage of hypoglycemic agents.

Methotrexate: Caution should be exercised if NSAIDs and methotrexate are administered within 24 hours of each other, since NSAIDs may increase plasma levels, resulting in increased toxicity.

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

Corticosteroids: Concomitant administration of aceclofenac with corticosteroids may increase the risk of GI ulceration or bleeding.

Anti-Platelet Agents and Selective Serotonin Reuptake Inhibitors (SSRIs): Concomitant administration of aceclofenac with these drugs may increase the risk of GI bleeding.

Ciclosporin: Ciclosporin nephrotoxicity may be increased by the effect of NSAIDs on renal prostaglandins.

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 a NSAID.

<u>Paracetamol</u>

Cholestyramine: The rate of absorption of paracetamol is reduced by cholestyramine. Therefore, cholestyramine should not be taken within one hour, if maximal analgesia is required.

Metoclopramide and Domperidone: The absorption of paracetamol is increased by metoclopramide and domperidone. However, concurrent use need not be avoided.

Warfarin: The anti-coagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

Chloramphenicol: Concurrent administration of paracetamol and chloramphenicol may markedly retard the elimination of chloramphenicol and thus, increases plasma concentration of

chloramphenicol which leads to risk of its harmful effects. Monitoring of chloramphenicol plasma levels is recommended while combining paracetamol with chloramphenicol injection.
Alcohol, Anticonvulsants, and Isoniazid: Concomitant administration of alcohol, anticonvulsants, and isoniazid with paracetamol may increase risk of hepatotoxicity.

Serratiopeptidase
Anticoagulant/Antiplatelet Drugs: If administered along with warfarin, clopidogrel, or aspirin, there may be increased risk of bleeding or bruising.
Natural Substances: There may be increased risk of bleeding or bruising when serratiopeptidase is administered with other natural substances such as garlic, fish oil and turmeric.

4.6Use in Special Populations

Pregnant Women
For this combination product, there are no adequate and well controlled studies available in pregnant women. Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage. Not enough is known about the use of serratiopeptidase during pregnancy. Also, there is no information on the use of aceclofenac during pregnancy. However, use of NSAIDs during the last trimester of pregnancy may decrease uterine tone and contraction. It may also delay onset of labour and increase its duration. NSAID use may also result in premature closure of the foetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the new born, delay onset and increase duration of labour. Being an NSAID, these effects cannot be ruled out with aceclofenac. Based on its aceclofenac content, DOLOSTAT-SP Tablets should not be used during the first two trimesters of pregnancy or labor unless the potential benefit to the patient outweighs the possible risk to fetus. Further, DOLOSTAT-SP Tablets are contraindicated in the third trimester (> 30 weeks of gestation) of pregnancy.

Lactating Women
Paracetamol is excreted in breast milk, but not in significant amounts. Not enough is known about the use of serratiopeptidase during lactation. There is no information on the secretion of aceclofenac in human milk. However, in limited studies so far available, NSAIDs can appear in breast milk in very low concentrations. Because of the potential for serious adverse reactions in nursing infants with NSAIDs, a decision should be made whether to discontinue nursing or to discontinue the drug therapy, taking into account the importance of the drug to the mother.

Paediatric Patients
Safety and effectiveness of this formulation has not been established in paediatric population. Thus, DOLOSTAT-SP Tablets are not recommended for use in children.

Geriatric Patients

Elderly patients with normal renal and hepatic function and without gastrointestinal (GI) disorders may be given the same dose as recommended for adults. Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. Thus, DOLOSTAT-SP Tablets should be used with caution and patients should be monitored for adverse effects.
Paracetamol is mainly excreted by the kidney, and the risk of adverse reactions to paracetamol may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Renal Impairment Patients
DOLOSTAT-SP Tablets are contraindicated in patients with severe renal impairment or in patients with preexisting renal disease. Paracetamol is mainly excreted by renal route; therefore, this product should be used with caution in patients with renal dysfunction (mild to moderate renal impairment). Further, in all cases of renal dysfunction, frequent monitoring of renal function is suggested. If required, longer dosing interval and a reduction in total daily dose should be considered.

Hepatic Impairment Patients
DOLOSTAT-SP Tablets should not be used in patients with active hepatic disease or hepatitis; further, its use is contraindicated in patients with severe hepatic impairment. DOLOSTAT-SP Tablets should be used cautiously, if at all, in patients with a previous history of liver disease. Also, it is suggested that an initial once daily dose of DOLOSTAT-SP Tablets should be considered in patients with mild to moderate hepatic impairment.

4.7Effect on Ability to Drive and Use Machines
Undesirable effects such as dizziness, vertigo, drowsiness, fatigue, visual disturbances or other central nervous system disorders are possible after taking NSAIDs, including aceclofenac. If affected, patients should not drive or operate machinery.

4.8Undesirable Effects
Aceclofenac
The majority of adverse reactions reported have been reversible and of a minor nature. The most frequent are GI disorders, in particular dyspepsia, abdominal pain, nausea and diarrhoea, and occasional dizziness.
If serious adverse reactions occur, aceclofenac should be withdrawn.
Gastrointestinal: The most commonly observed adverse events are GI in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melena, hematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease have been reported following

administration. Less frequently, gastritis has been observed. Pancreatitis has been reported very rarely.

Hypersensitivity: Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of a non-specific allergic reaction and/or anaphylaxis or respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnea.

Cardiovascular and Cerebrovascular: Edema, hypertension, palpitation, flushing, hot flushes, vasculitis and cardiac failure have been reported in association with NSAID treatment. Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (e.g., myocardial infarction or stroke).

Neurological and Special Senses: Optic neuritis, somnolence, reports of aseptic meningitis (especially in patients with existing auto immune disorders, such as systemic lupus erythematosus, mixed connective tissue disease) with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation, malaise, confusion, and drowsiness.

Renal: Interstitial nephritis.

Hematological: Agranulocytosis, aplastic anaemia.

Miscellaneous: In patients with varicella, serious cutaneous and soft tissue infections have been reported in association with NSAID treatment.

Other rarely reported adverse reactions of aceclofenac include the following:

Renal and Urinary: Renal insufficiency, abnormal serum creatinine levels, increased blood urea, renal failure, nephrotic syndrome.

Respiratory: Dyspnea, bronchospasm, stridor.

Hepatic: Abnormal hepatic enzyme levels, hepatitis, jaundice, increased blood alkaline phosphatase.

Blood and Lymphatic System: Anemia, bone marrow depression, granulocytopenia, thrombocytopenia, neutropenia, hemolytic anemia.

Skin and Subcutaneous Tissue Disorders: Pruritus, rash, photosensitivity reactions, dermatitis, urticaria, angioedema, purpura, erythema multiforme, exfoliative dermatitis, bullous dermatoses, severe mucocutaneous skin reactions (including Stevens-Johnson Syndrome - SJS and Toxic Epidermal Necrolysis - TEN).

Ear and Labyrinth Disorders: Tinnitus, vertigo.

Eye Disorders: Visual disturbance.

Nervous System: Paraesthesia, tremor, somnolence, headache, dysgeusia.

Psychiatric Disorders: Depression, abnormal dreams, confusion, hallucinations, insomnia.

Metabolism: Hyperkalemia.

General Disorders: Edema, fatigue, leg cramps.

Paracetamol

Adverse effects of paracetamol are rare. However, hypersensitivity including skin rash and fixed drug eruption (FDE) may occur. There have been reports of blood dyscrasias including

thrombocytopenic purpura, methemoglobenemia and agranulocytosis, but these were not necessarily related to paracetamol.

Serratiopeptidase

Serratiopeptidase is generally well tolerated. Some of the adverse effects reported with serratiopeptidase are skin reactions such as rash or redness, hypersensitivity, muscle and joint pain, anorexia, nausea, vomiting, abdominal discomfort, diarrhoea, cough, epistaxis and haemoptysis.

4.9Overdose

Aceclofenac

Symptoms: There are no human data available on the consequences of aceclofenac overdose. Symptoms of overdose include headache, nausea, vomiting, epigastric pain, GI irritation, GI bleeding. Rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, hypotension, respiratory depression, fainting, and occasionally convulsions may occur. In cases of significant poisoning acute renal failure and liver damage are possible.

Treatment: If overdose with aceclofenac occurs, absorption should be prevented as soon as possible by means of gastric lavage and treatment with activated charcoal. Supportive and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, GI irritation, and respiratory depression. Specific therapies such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs due to their high rate of protein binding and extensive metabolism. Renal and liver function should be closely monitored.

Paracetamol

Symptoms: Ingestion of 5 gram or more of paracetamol may lead to liver damage. Symptoms of paracetamol overdose in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, hemorrhage, hypoglycaemia, cerebral edema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, hematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Treatment: Immediate treatment is essential in the management of paracetamol overdose. Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine (approved antidote) may be used up to 24 hours after ingestion of paracetamol. However, the maximum protective effect is obtained up to 8 hours post ingestion.

Serratiopeptidase

Symptoms: Nausea, vomiting, discomfort in epigastria. In some cases blood may streak in phlegm and cause bleeding.

Treatment: There is no known antidote for serratiopeptidase. In case of overdose, withdrawal from the therapy is recommended. Patients should be referred to hospital urgently for immediate medical attention. Treatment should be symptomatic and supportive.

5. Pharmacological Properties

5.1 Mechanism of Action

Aceclofenac

The mode of action of aceclofenac is largely based on the inhibition to prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclooxygenase (COX). COX enzymes are involved in conversion of arachidonic acid into prostaglandin (PGs). Prostaglandins are usually responsible for causing pain, inflammation, and fever. Aceclofenac blocks the enzyme COX and thereby inhibit PGs synthesis, thus, produces analgesic and anti-inflammatory effects.

Paracetamol

Analgesic Effect: The mechanism of analgesic action of paracetamol has not been fully determined. Paracetamol may act predominantly by inhibiting prostaglandin synthesis in the central nervous system (CNS) and to a lesser extent, through a peripheral action by blocking pain-impulse generation. The peripheral action may also be due to inhibition of prostaglandin synthesis or inhibition of the synthesis or actions of other substances that sensitise pain receptors to mechanical or chemical stimulation.

Antipyretic Effect: Paracetamol produces antipyretic effect by acting centrally on the hypothalamic heat-regulation center to produce peripheral vasodilation resulting in increased blood flow through the skin, sweating and heat loss. The central action involves inhibition of prostaglandin synthesis in the hypothalamus.

Serratiopeptidase

Anti-inflammatory Effect: Anti-inflammatory activity of serratiopeptidase has been attributed to hydrolysis of inflammatory mediators such as bradykinin, histamine, and serotonin. It may also act by modifying cell-surface adhesion molecules that guide inflammatory cells to their target site of inflammation.

Analgesic Effect: Serratiopeptidase may help alleviate pain by inhibiting the release of pain-inducing amines like bradykinin from inflamed tissues.

Anti-edemic Effect: Serratiopeptidase reduces swelling by the process of decreasing the amount of fluid in the tissues, thinning the fluid, and by facilitating the drainage of fluid. In addition, enzyme activity of serratiopeptidase dissolves dead tissue surrounding the injured area to accelerate the healing process.

5.2Pharmacodynamic Properties

Aceclofenac

Aceclofenac is a non-steroidal anti-inflammatory drug (NSAID) with marked analgesic and anti-inflammatory properties.

Paracetamol

Paracetamol is a centrally acting analgesic and antipyretic agent.

Serratiopeptidase

Serratiopeptidase also known as serrapeptase is a proteolytic enzyme derived from bacterium *Serratia E-15 spp*. This bacterium was originally isolated from intestine of silkworm *Bombyx mori L*. Serratiopeptidase has been used for reducing swelling and inflammation associated with surgery, trauma, infection, and other inflammatory conditions. Serratiopeptidase possesses anti-inflammatory, analgesic, and anti-edemic properties.

5.3Pharmacokinetic Properties

Aceclofenac

After oral administration, aceclofenac is rapidly and completely absorbed as unchanged drug. Peak plasma concentrations are reached approximately 1.25 to 3.00 hours following ingestion. Aceclofenac penetrates into the synovial fluid, where the concentrations reach approximately 57% of those in plasma. The volume of distribution is approximately 25 liters. The mean plasma elimination half-life is around 4 hours. Aceclofenac is highly protein-bound (>99%). Aceclofenac circulates mainly as unchanged drug. The main metabolite detected in plasma is 4'-hydroxyaceclofenac. Approximately two- thirds of the administered dose is excreted via the urine, mainly as hydroxymetabolites. No changes in the pharmacokinetics of aceclofenac have been detected in the elderly.

Paracetamol

Paracetamol is readily absorbed from the GI tract with peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion. Paracetamol is metabolized in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life varies from about 1 to 4 hours. Plasma protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

Serratiopeptidase

Serratiopeptidase when administered in unprotected form is destroyed by acid in the stomach. Enteric coated granule formulation, enable the serratiopeptidase to pass through the stomach unchanged and reach in the intestine. Orally administered serratiopeptidase (in the form of enteric coated granules) has been shown to be absorbed unchanged from the small intestine and reaches into the systemic circulation in enzymatically active form. From circulation, serratiopeptidase

penetrates into all the tissues. It reaches higher concentrations in the inflamed tissues. Peak plasma concentration occurs in one hour. Metabolism of serratiopeptidase takes place in the liver. The metabolites of serratiopeptidase are excreted through the urine and faeces.

6. Nonclinical Properties

6.1 Animal Toxicology

Aceclofenac

Aceclofenac was not considered to have any mutagenic activity in three in vitro studies and an in vivo study in the mouse.

Aceclofenac was not found to be carcinogenic in either the mouse or rat.

Animal studies indicate that there was no evidence of teratogenesis in rats although the systemic exposure was low and in rabbits, treatment with aceclofenac (10 mg/kg/day) resulted in a series of morphological changes in some fetuses.

Paracetamol

Preclinical data reveal no special hazard for humans with paracetamol based on conventional studies of single and repeated dose toxicity, genotoxicity and carcinogenicity. Studies for the evaluation of toxicity to reproduction and development are not available.

Serratiopeptidase

No information on preclinical toxicology or pharmacology is available for serratiopeptidase.

7. Description

DOLOSTAT-SP Tablets are orange coloured, Capsule shaped, biconvex & one side scored, film coated tablet .

Each tablet of DOLOSTAT-SP contains 100 mg of aceclofenac, 325 mg of paracetamol, and 15 mg of serratiopeptidase for oral administration in adults.

Aceclofenac

Aceclofenac is a monocarboxylic acid that is the carboxymethyl ester of diclofenac. Aceclofenac is an oral non-steroidal anti-inflammatory drug (NSAID) with marked anti-inflammatory and analgesic properties.

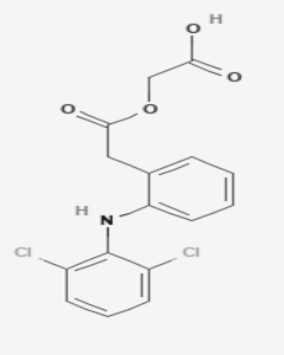
Aceclofenac is available in white crystalline powder.

Molecular Weight: 354.2 g/mol.

Chemical Name: 2-[2-[2-(2,6-dichloroanilino)phenyl]acetyl]oxyacetic acid.

Molecular Formula: $C_{16}H_{13}Cl_2NO_4$.

Structural Formula:



Paracetamol

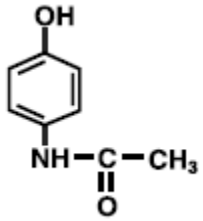
Paracetamol, also called as acetaminophen, is a slightly bitter, white, odorless, crystalline powder. Paracetamol is a non-opiate, non-salicylate analgesic and antipyretic agent.

Molecular Weight: 151.16 g/mol.

Chemical Name: 4'-hydroxyacetanilide.

Molecular Formula: C8H9NO2.

Structural Formula:



Serratiopeptidase

Serratiopeptidase, also known as serrapeptase, is a proteolytic enzyme having anti-inflammatory and anti-edemic effects. Serratiopeptidase is isolated initially from the Enterobacteria *Serratia marcescens* strain E-15 found in the gut of the Japanese silkworm Bombyx mori. Serratiopeptidase has an affinity to the dead proteins. Serratiopeptidase does not affect healthy tissues in the body because the chemical structure of serratiopeptidase inhibits attachment to proteins in healthy tissues. Serratiopeptidase is an active enzyme that binds to the α-2 macroglobulin in biological fluids and in blood; it binds in the ratio of 1:1 and this binding helps mask its antigenicity, retaining the enzymatic activity.

The molecular weight of serratiopeptidase ranges about 45 kDa to 60 kDa. It is a metalloprotease and contains three zinc atoms as ligands and one active site. The presence of zinc atom is essential and also enhances the proteolytic activity of serratiopeptidase.

The gene encoding serratiopeptidase reveals that it is made up of 470 amino acids. The amino acid sequence is free of sulfur containing amino acids, cysteine and methionine. The maximum enzyme activity of serratiopeptidase is observed at pH 9.0 and at a temperature of 40°C. Serratiopeptidase is degraded or inactivated completely at a temperature of 55°C.

Inactive ingredients (excipients) of DOLOSTAT-SP Tablets contains Lactose, Microcrystalline Cellulose, Maize Starch, Croscarmellose Sodium, Polyvinyl Pyrrolidone, Methyl Paraben, Propyl Paraben, Colloidal Silicon Dioxide, Magnesium Stearate, Colour Sunset Yellow FCF, Talcum, Titanium Dioxide, and Hydroxy Propyl Methyl Cellulose.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

24 months.

8.3Packaging Information

10 tablets per strip.

8.4Storage and Handling Instructions

Store protected from light and moisture, at a temperature not exceeding 30°C.
Keep out of reach of children.

9. Patient Counseling Information

Instructions to Patients

- Instruct patients to use this medicine exactly as prescribed, at the lowest dose possible, and for the shortest time needed (as it contain NSAID i.e., aceclofenac). Usually, 1 tablet of DOLOSTAT-SP to be taken twice daily preferably 2 hours after a meal. The tablet should be swallowed whole with water and strictly not to be cut, crushed or chewed.
- Patients should be advised that this medicine may increase the chance of a heart attack or stroke as it contains NSAID class of drug i.e., aceclofenac. This chance increases with longer use of NSAID medicines and in people who have heart disease.
- Patients should be informed that NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding can happen without warning symptoms.
- Do not take an NSAID medicine if you had an asthma attack, urticaria/itching, or other allergic reaction with aspirin or any other NSAID medicine.
- Not to use with any other drug containing paracetamol (prescription or over-the- counter - OTC). Users to ask a doctor or pharmacist, if they are not sure about presence of paracetamol in the drug taken for other illnesses.
- Pregnant women should avoid use of NSAID medicines especially in the last 3 months of pregnancy. Breastfeeding mothers are advised not to use this medicine.

- Advise patient to discontinue therapy at least 2 weeks before a scheduled surgery (as it contains serratiopeptidase).

10. Details of Manufacturer

Akums Drugs & Pharmaceuticals Ltd.
Plot No. 26A, 27-30, Sector-8A, I.I.E., SIDCUL,
Ranipur, Haridwar – 249 403, Uttarakhand.

11. Details of Permission or License Number with Date

Mfg. Lic. No. : 8/UA/LL/SC/P-2014; Date of FDA Product Permission: 15/09/2015.

12. Date of Revision

February 2023.

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