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 (SR) & Rabeprazole (GR) Capsules
(Brand Name: DOLOSTAT®+ R Capsules)

2. Qualitative and Quantitative Composition

Each hard gelatin capsule contains:
Aceclofenac IP ……. 200 mg.
(as sustained release tablet)
Rabeprazole Sodium IP ……..…… 20 mg.
(as gastro-resistant tablet)
Colours: Red Oxide of Iron & Titanium Dioxide IP.
Excipients …… q.s.
Colours used in capsule shell: Erythrosine, Tartrazine, Titanium Dioxide IP.
Methylparaben and Proylparaben used as antimicrobial preservatives.

3. Dosage Form and Strength

Dosage Form: Capsules.
Dosage Strength: Aceclofenac 200 mg (in a sustained release tablet form) and rabeprazole 20 mg (as gastro-resistant tablet) per capsule.

4. Clinical Particulars

4.1 Therapeutic Indication

DOLOSTAT+R Capsules are indicated for relief of pain and inflammation in musculoskeletal disorders such as rheumatoid arthritis, osteoarthritis and ankylosing spondylitis in adult patients with a history of peptic ulcer or those at increased risk for non-steroidal anti-inflammatory drug (NSAID)-induced gastrointestinal (GI) toxicity.

4.2Posology and Method of Administration

For oral administration in adults.
Usual Dose: 1 capsule of DOLOSTAT+ R to be administered once daily. Duration of therapy depends on type and severity of the inflammatory condition treated.

Generally, DOLOSTAT+ R Capsules should be administered with food so as to reduce the NSAID-associated gastropathy/GI intolerance. The capsule should be swallowed whole with water and not to be cut, crushed or chewed.
Or, as prescribed by the physician.

4.3Contraindications

DOLOSTAT+ R Capsules are contraindicated in the following:

- Known hypersensitivity to aceclofenac or to rabeprazole (substituted benzimidazoles) 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 hepatic impairment.
- Patients with established congestive heart failure (NYHA class II-IV), ischemic heart disease, severe heart failure, peripheral arterial disease and/or cerebrovascular disease.
- Pregnancy.
- Breast-feeding.
- Patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by aspirin or other NSAIDs.
- Rilpivirine-containing (anti-HIV) products (due to its rabeprazole content).

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 -PPIs) 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.

Rabeprazole
Presence of Gastric Malignancy: Symptomatic response to therapy with rabeprazole does not preclude the presence of gastric or esophageal malignancy, therefore, the possibility of malignancy should be excluded prior to commencing treatment with rabeprazole. Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.
Hypersensitivity: A risk of cross-hypersensitivity reactions with substituted benzimidazoles cannot be excluded.
Acute Interstitial Nephritis: Acute interstitial nephritis has been observed in patients taking PPIs, including rabeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue rabeprazole-containg therapy if acute interstitial nephritis develops.
Cyanocobalamin (vitamin B12) Deficiency: Daily treatment with acid-suppressing medicines over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria.
Hypomagnesemia: Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement as well as discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), it is recommended to monitor magnesium levels prior to initiation of PPI treatment and then periodically while treatment continues.
Fractures: Observational studies suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, and long-term PPI therapy (a year or longer).
***Clostridium Difficile*-Associated Diarrhea (CDAD):** Treatment with PPIs, including rabeprazole, may possibly increase the risk of gastrointestinal infections caused by bacteria such as Salmonella, Campylobacter and *Clostridium difficile*. PPI therapy (i.e., rabeprazole) may be associated with an increased risk of *Clostridium difficile*-associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve.
Subacute Cutaneous Lupus Erythematosus (SCLE): SCLE has been reported with the use of PPIs. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by

arthralgia, the patient should seek medical help promptly and stop rabeprazole-containing therapy. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs.

4.5Drug Interactions

Aceclofenac

Lithium: Aceclofenac, like many NSAIDs, may increase plasma concentration of lithium and thus, increases their 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.

Rabeprazole

Drugs Dependent on Gastric pH for Absorption (e.g., iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetil, ketoconazole, itraconazole): Rabeprazole can reduce the absorption of these drugs due to its effect on reducing intragastric acidity.

Ketoconazole or Itraconazole: Co-administration of rabeprazole with ketoconazole or itraconazole may result in a significant decrease in antifungal plasma levels. A 33% decrease in ketoconazole levels was observed in normal subjects given both drugs concomitantly. Therefore individual patients may need to be monitored to determine if a dosage adjustment is necessary when ketoconazole or itraconazole are taken concomitantly with rabeprazole.

Methotrexate: Literature suggests that concomitant use of PPIs with methotrexate (primarily at high doses) may elevate and prolong serum levels of methotrexate and/or its metabolite (hydroxymethotrexate), possibly leading to methotrexate toxicity. During high-dose methotrexate therapy, a temporary withdrawal of the PPI may be considered in some patients.

Digoxin: A 22% increase in trough digoxin levels was observed in normal subjects given both drugs concomitantly. Monitor digoxin concentrations. Dose adjustment of digoxin may be needed to maintain therapeutic drug concentrations.

Antiretrovirals: The effect of PPI on antiretroviral drugs is variable. The clinical importance and the mechanisms behind these interactions are not always known.

Atazanavir: Co-administration of atazanavir with other PPIs has resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH-dependent. Therefore PPIs, including rabeprazole, should not be co-administered with atazanavir.

Rilpivirine-Containing Products: Concomitant use with rabeprazole is contraindicated.

Mycophenolate Mofetil: Co-administration of PPIs with mycophenolate mofetil in healthy and transplant patients has been reported to reduce exposure to the active metabolite, mycophenolic acid. This is possibly due to a decrease in mycophenolate mofetil solubility at an increased gastric pH. The clinical relevance of reduced mycophenolic acid exposure on organ rejection has not been established in transplant patients receiving PPIs and mycophenolate mofetil. Rabeprazole-containing products should be used cautiously in transplant patients receiving mycophenolate mofetil.

Clopidogrel: Clopidogrel is metabolised to its active metabolite by CYP2C19. Inhibition of CYP2C19 by rabeprazole would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in its antiplatelet activity and therefore, its clinical efficacy. Concomitant use of rabeprazole-containing products with clopidogrel should be avoided.

Warfarin: An increase in INR and prothrombin time has been reported in patients receiving PPIs, including rabeprazole, and warfarin concomitantly. Increases in INR and prothrombin time may

lead to abnormal bleeding and even death. Monitor INR and prothrombin time. Dose adjustment of warfarin may be needed to maintain target INR range.

Tacrolimus: Potentially increased exposure of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19. Monitor tacrolimus whole blood trough concentrations. Dose adjustment of tacrolimus may be needed to maintain therapeutic drug concentrations.

Interference with Laboratory Tests: Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, rabeprazole treatment should be stopped for at least 5 days before CgA measurements. If CgA and gastrin levels have not returned to reference range after initial measurement, assessments should be repeated 14 days after cessation of PPI treatment.

False Positive Urine Tests for THC: There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving PPIs. An alternative confirmatory method should be considered to verify positive results.

4.6Use in Special Populations

Pregnant Women

Aceclofenac: Pregnancy Category C; Rabeprazole: Pregnancy Category C. There is no clinical information available on the use of aceclofenac-rabeprazole combination therapy during pregnancy. Congenital abnormalities have been reported with the use of NSAIDs in humans. 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 fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the new born, delay onset and increase duration of labour.

There are no data on the safety of rabeprazole in human pregnancy. Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole, although low feto-placental transfer occurs in rats.

DOLOSTAT+ R Capsules are contraindicated during pregnancy.

Lactating Women

There is no information on the secretion of aceclofenac in human milk. Lactation studies have not been conducted to assess the presence of rabeprazole in human milk, the effects of rabeprazole on the breastfed infant, or the effects of rabeprazole on milk production. However, rabeprazole is present in rat milk. DOLOSTAT+ R Capsules should not be used during breastfeeding. Accordingly, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Paediatric Patients

Safety and efficacy of aceclofenac has not been established and thus, it is not advocated in children. Rabeprazole 20 mg is not recommended for use in paediatric patients below 12 years of age. Thus, DOLOSTAT+ R Capsules are not recommended in paediatric population.

Geriatric Patients

There are no data to suggest that aceclofenac dosage should be reduced in the elderly, however, as with other NSAIDs, caution should be exercised. The elderly have an increased frequency of adverse reactions to NSAIDs, especially GI bleeding and perforation which may be fatal. With rabeprazole, no overall differences in safety or effectiveness were observed between elderly and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Elderly patients with normal renal and hepatic function should be given the same dose as recommended for adults.

Renal Impairment Patients

In patients with renal impairment, no dosage adjustment is necessary with rabeprazole. No need to modify the aceclofenac dosage in patients with mild renal impairment, but as with other NSAIDs, caution should be exercised. DOLOSTAT+ R Capsules may be used in patients with renal dysfunction, but with caution.

Hepatic Impairment Patients

Administration of rabeprazole to patients with mild to moderate hepatic impairment resulted in increased exposure and decreased elimination. However, no dosage adjustment is necessary in these patients. There is no information in patients with severe hepatic impairment and thus, use of rabeprazole should be avoided in such patients. In patients with hepatic impairment, aceclofenac dose should be reduced to 100 mg daily. There is no possibility of dosage feasibility with this formulation. Thus, DOLOSTAT+ R Capsules are not recommended for use in patients with any degree of hepatic impairment.

4.7Effect on Ability to Drive and Use Machines

Rabeprazole is unlikely to cause an impairment of driving performance or compromise the ability to use machinery. However, undesirable effects such as dizziness, vertigo, drowsiness, fatigue, visual disturbances or other central nervous system disorders are possible after taking NSAIDs, including aceclofenac. If alertness is impaired due to somnolence, 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 also been reported. 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 anemia.
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 System: Renal insufficiency, abnormal serum creatinine levels, increased blood urea, renal failure, nephrotic syndrome.
Respiratory System: Dyspnea, bronchospasm, stridor.
Hepatic Disorders: 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: Pruritus, rash, photosensitivity reactions, dermatitis, urticaria, angioedema, purpura, erythema multiforme, exfoliative dermatitis, bullous dermatoses severe mucocutaneous skin reactions (including Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis).
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.

Rabeprazole

Rabeprazole is generally well tolerated. The reported side effects have generally been mild or moderate and transient in nature.

Clinical Trials Experience

Adverse reactions appearing in 2 to 3 % of patients treated with rabeprazole and with a greater frequency than placebo in controlled clinical trials (acute therapy) include the following: Pain, pharyngitis, flatulence, infection, and constipation.
Less common (<2%) adverse reactions seen in controlled clinical trials in patients treated with rabeprazole and for which there is a possibility of a causal relationship to rabeprazole, include the following: Headache, abdominal pain, diarrhea, dry mouth, dizziness, peripheral edema, hepatic enzyme increase, hepatitis, hepatic encephalopathy, myalgia, and arthralgia.

Post-Marketing Experience

The following adverse reactions have been identified during post approval use of rabeprazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:
Blood and Lymphatic System: Agranulocytosis, hemolytic anemia, leukopenia, pancytopenia, thrombocytopenia.
Ear and Labyrinth Disorders: Vertigo.
Eye Disorders: Blurred vision.
Hepatobiliary Disorders: Jaundice.
Immune System: Anaphylaxis, angioedema, systemic lupus erythematosus, Stevens-Johnson syndrome, toxic epidermal necrolysis (may be fatal).
Infections and Infestations: *Clostridium difficile*-associated diarrhea.
Metabolism and Nutrition Disorders: Hyperammonemia, hypomagnesemia.
Musculoskeletal System: Bone fracture, rhabdomyolysis.
Psychiatric Disorders: Delirium, disorientation.
Renal and Urinary System: Interstitial nephritis.
Respiratory, Thoracic and Mediastinal Disorders: Interstitial pneumonia.
Skin and Subcutaneous Tissue: Severe dermatologic reactions including bullous and other drug eruptions of the skin, cutaneous lupus erythematosus, erythema multiforme.
Laboratory Tests: Increase in prothrombin time/INR (in patients treated with concomitant warfarin), elevations in thyroid stimulating hormone (TSH).

4.9Overdose

Aceclofenac

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, occasionally and convulsions may occur. In cases of significant poisoning acute renal failure and liver damage are possible.

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.

Rabeprazole

Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile and reversible without further medical intervention. Rabeprazole is extensively protein bound and is, therefore, not readily dialyzable. No specific antidote for rabeprazole is known. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilized.

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.

Rabeprazole

Rabeprazole blocks the final step of gastric acid secretion by inhibiting the gastric H+, K+ ATPase (proton pump) at the secretory surface of the gastric parietal cell. Because this enzyme is regarded as the acid (proton) pump within the parietal cell, rabeprazole has been characterized as a gastric proton-pump inhibitor. Thus, by inhibiting/blocking proton pumps at parietal cell surface, rabeprazole reduces hydrochloric acid (HCl) production in the stomach.

5.2Pharmacodynamic Properties

Aceclofenac

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

Rabeprazole

Rabeprazole belongs to a class of antisecretory compounds (substituted benzimidazole PPI). Rabeprazole significantly reduces hydrochloric acid production in the stomach. Rabeprazole reduces hyperacidity and treat gastrointestinal (GI) disorders such as peptic ulcers and gastroesophageal reflux disease (GERD). When rabeprazole is co-administered with NSAIDs, it prevents or reduces risk of GI irritation and ulcers or GERD associated with NSAIDs.

5.3Pharmacokinetic Properties

Aceclofenac (Immediate Release - IR Tablets)

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.

Comparison of Aceclofenac 200 mg (SR) vs. Aceclofenac 100 mg (IR)

The results from pharmacokinetic studies demonstrate that aceclofenac 200 mg sustained release (SR) tablet is equivalent to aceclofenac 100 mg immediate-release (IR) tablets when administered at the same total daily dose. The area under the plasma concentration-time curve (AUC_{0-24}) and the peak plasma concentration (C_{max}) of aceclofenac for the SR and IR formulations of aceclofenac are within the bioequivalence criteria range of 80 to 125%. Pharmacokinetic data suggest that aceclofenac SR formulation (200 mg) and the aceclofenac IR formulation (100 mg) are bioequivalent. However, the SR formulation exhibited a longer elimination half-life (t½) and delayed T_{max}, demonstrating sustained release properties of aceclofenac.

Rabeprazole – Gastro Resistant (enteric-coated) Tablets

Absorption: Rabeprazole is rapidly absorbed and peak plasma concentrations are reached about 3.5 hours after an oral dose. The oral bioavailability is about 52% with the enteric-coated tablet formulation, because of first-pass metabolism, and does not appear to vary after single or repeated doses.

Distribution: Rabeprazole is about 97% bound to plasma proteins.

Metabolism: Rabeprazole is extensively metabolised in the liver by cytochrome P450 isoenzymes CYP2C19 and CYP3A4 to the thioether, thioether carboxylic acid, sulfone, and desmethylthioether derivatives.
Excretion: Metabolites are excreted principally in the urine (about 90%) with the remainder in the faeces. The plasma half-life is about 1 hour which increases 2 to 3-fold in hepatic impairment, 1.6 times in CYP2C19 slow metabolisers, and by 30% in the elderly.

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.

Rabeprazole

Carcinogenesis: In an 88/104-week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumor occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 μg•hr/ml which is 1.6 times the human exposure (plasma $AUC_{0-\infty}$ = 0.88 μg•hr/ml) at the recommended dose for GERD (20 mg/day). In a 28-week carcinogenicity study in p53+/- transgenic mice, rabeprazole at oral doses of 20, 60, and 200 mg/kg/day did not cause an increase in the incidence rates of tumors but produced gastric mucosal hyperplasia at all doses. The systemic exposure to rabeprazole at 200 mg/kg/day is about 17 to 24 times the human exposure at the recommended dose for GERD.
Mutagenesis: Rabeprazole was positive in the Ames test, the Chinese hamster ovary cell (CHO/HGPRT) forward gene mutation test, and the mouse lymphoma cell (L5178Y/TK+/–) forward gene mutation test. Its demethylated-metabolite was also positive in the Ames test. Rabeprazole was negative in the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test, and the *in vivo* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.
Impairment of Fertility: Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 μg•hr/ml, about 10 times the human exposure at the recommended dose for GERD) was found to have no effect on fertility and reproductive performance of male and female rats.
Teratogenicity: Embryo-fetal developmental studies have been performed in rats during organogenesis at intravenous doses of rabeprazole up to 50 mg/kg/day (plasma AUC of 11.8 μg•hr/ml, about 13 times the human exposure at the recommended oral dose for GERD) and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 μg•hr/ml, about 8 times the human

exposure at the recommended oral dose for GERD) and have revealed no evidence of harm to the fetus due to rabeprazole.

7. Description

DOLOSTAT+R Capsules are orange/white hard gelatin capsules of size "0" containing one brown coloured enteric coated tablet of Rabeprazole Sodium & two white sustained release tablets of aceclofenac tablets.

Each capsule of DOLOSTAT+R contains 200 mg of aceclofenac (in sustained release tablet form) and 20 mg of rabeprazole (in gastro-resistant tablet form) 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.

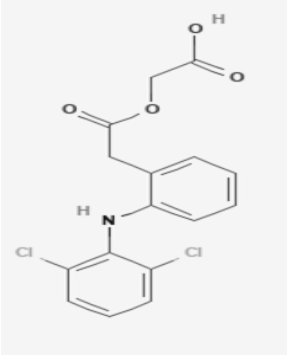
Aceclofenac is available in white crystalline powder.

Molecular Weight: 354.2 g/mol.

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

Molecular Formula: C16H13Cl2NO4.

Structural Formula:



Rabeprazole Sodium

Rabeprazole is a substituted benzimidazole, proton pump inhibitor (PPI) class of antisecretory drugs.

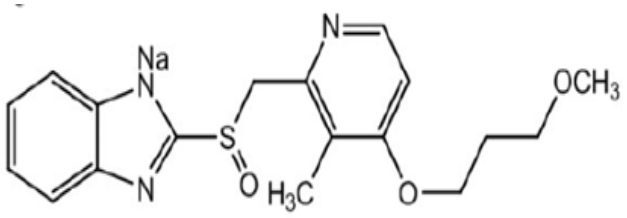
Rabeprazole sodium is a white to slightly yellowish-white solid. It is very soluble in water and methanol, freely soluble in ethanol, chloroform, and ethyl acetate and insoluble in ether and n-hexane.

Molecular Weight: 381.42 g/mol.

Chemical Name: 2-[[[4-(3methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfinyl]-1H–benzimidazole sodium salt.

Molecular Formula: C18H20N3NaO3S.

Structural Formula:



Inactive ingredients (excipients) of DOLOSTAT+R Capsule contains Light Magnesium Oxide, Mannitol, Crospovidone, Hydroxy Propyl Cellulose, Magnesium Stearate, Talcum, Crosscarmellose Sodium, Hydroxy Propyl Methyl Cellulose, Ethyl Cellulose, Polyethylene Glycol, Sodium Methyl Paraben, Colour Iron Oxide of Red, Acrylate Copolymers, Cellulose Acetate Phthalate, Methacrylic Acid and Ethyl Acrylate Co-polymer, Triethyl Citrate, Sodium Bicarbonate, Sodium Lauryl Sulfate, Titanium Dioxide, Polyvinyl Pyrrolidone, and Hard Gelatin Capsule.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

24 months.

8.3Packaging Information

10 capsules 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 and advised by your doctor. Usually, 1 capsule of DOLOSTAT+ R to be taken once daily with food (to reduce risk of GI intolerance associated with aceclofenac).
- If you miss a dose, take it as soon as possible. If it is almost time for your next dose, you should not take the missed dose. Instead, take your next dose at regular time. Do not take 2 doses at the same time.

- Instruct patients to swallow capsules whole with water and not to cut, crush or chew.
- 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.
- 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.
- Pregnant women should avoid use of NSAID medicines especially in the last 3 months of pregnancy.
- Advice lactating mothers not to use this medicine while breastfeeding.

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. : 4/UA/LL/2014; Date of FDA Product Permission: 21/04/2016.

12. Date of Revision

April 2021.

Marketed by:
EXCEL BLUE CROSS || EXCEL
Division of
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