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

CHYMORAL-AP

1. Generic Name

Trypsin-Chymotrypsin with Paracetamol and Aceclofenac Tablets

2. Qualitative and quantitative composition

Each film coated tablet contains:

50000 Armour units of Enzymatic Activity (Supplied by a Purified Concentrate which has specific Trypsin & Chymotrypsin activity in a Ratio of Approximately Six to One)
(As enteric coated granules)

Paracetamol I.P. ……..325 mg

Aceclofenac I.P. ……..100 mg

Excipients…….q.s.

Colours: Quinoline Yellow Lake and Titanium Dioxide I.P.

The excipients used are Starch, Lactose, PVP-K-30, Methyl Paraben, Propyl Paraben, Seal coat SR 5003, Ethyl Cellulose, Crospovidone, Talcum, Magnesium Stearate, Super Coat (Film) and Titanium Dioxide.

3. Dosage form and strength

Dosage form: Film coated tablet

Strength: 50000 Armour units of Enzymatic Activity (Supplied by a Purified Concentrate which has specific Trypsin & Chymotrypsin activity in a Ratio of Approximately Six to One)

Paracetamol - 325 mg & Aceclofenac - 100 mg

4. Clinical particulars

4.1 Therapeutic indication

CHYMORAL-AP is used for acute or chronic osteoarthritis, rheumatoid arthritis and spondylo arthritis, spondylosis and other ortho-degenerative disorders, pain management

4.2 Posology and method of administration

Posology

Dose: The daily recommended dose is as directed by the Physician.

Method of administration

CHYMORAL-AP tablets should be administered orally. Do not crush or chew the tablet. Swallow as a whole.

4.3 Contraindications

- Hypersensitivity to trypsin-chymotrypsin or paracetamol or Aceclofenac or any of the other constituents.
- Severe liver problems, kidney impairment, peptic ulcer, high vitreous pressure, and hypersensitivity.
- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Hypersensitivity reactions (eg. Asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin, or other non-steroidal anti-inflammatory drugs.
- Hepatic failure and renal failure.
- Established congestive heart failure (NYHA II-IV), ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- History of gastrointestinal bleeding or perforation, related to previous NSAIDS therapy.
- Active bleedings or bleeding disorders.
- CHYMORAL-AP should not be prescribed during pregnancy, especially during the last trimester of pregnancy, unless there are compelling reasons for doing so. The lowest effective dosage should be used.

4.4 Special warnings and precautions for use

Trypsin-Chymotrypsin

- Rarely, chymotrypsin might cause an allergic reaction when taken by mouth. Symptoms include itching, shortness of breath, swelling of the lips or throat, shock, loss of consciousness, and death.
- Not to be used in patients with severe hepatic impairment or renal damage or irregularities of the blood clotting mechanism.

Paracetamol

- Underlying liver disease increases the risk or paracetamol related liver damage. Patients who have been diagnosed with liver or kidney impairment must seek medical advice before taking this medication.
- Do not exceed the stated dose. Patients should be advised to consult their doctor if their headaches become persistent. Patients should be advised to consult a doctor if they suffer from non-serious arthritis and need to take painkillers every day.
- Caution should be exercised in patients with glutathione depleted states, as the use of paracetamol may increase the risk of metabolic acidosis.
- Use with caution in patients with glutathione depletion due to metabolic deficiencies.
- If symptoms persist, medical advice must be sought.
- Keep out of the sight and reach of children.

Pack Label:

Talk to a doctor at once if you take too much of this medicine even if you feel well.

Do not take anything else containing paracetamol while taking this medicine.

Patient Information Leaflet:

Talk to a doctor at once if you take too much of this medicine even if you feel well. This is because too much paracetamol can cause delayed, serious liver damage.

Aceclofenac

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

The use of Aceclofenac with concomitant NSAIDs including cyclooxygenase- 2 selective inhibitors should be avoided.

Elderly:

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

Respiratory disorders:

Caution is required if administered to patients suffering from, or with a previous history of, bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients.

Cardiovascular, Renal and Hepatic Impairment:

The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics or recovering from major surgery, and the elderly. The importance of prostaglandins in maintaining renal blood flow should be taken into account in these patients.

Renal function should be monitored in these patients.

Renal:

Patients with mild to moderate renal impairment 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. Effects on renal function are usually reversible on withdrawal of Aceclofenac.

Hepatic:

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 Tablets should be discontinued. Close medical surveillance is necessary in patients suffering from mild to moderate impairment of hepatic function. Hepatitis may occur without prodromal symptoms.

Use of Aceclofenac in patients with hepatic porphyria may trigger an attack.

Cardiovascular and cerebrovascular effects:

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. Patients with congestive heart failure (NYHA-I) and patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with aceclofenac after careful consideration. As the cardiovascular risks of aceclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re- evaluated periodically.

Aceclofenac should also be administered with caution and under close medical surveillance to patients with a history of cerebrovascular bleeding.

Gastrointestinal 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.

Close medical surveillance is imperative in patients with symptoms indicative of gastro-intestinal disorders involving either the upper or lower gastrointestinal tract, with a history suggestive of gastro-intestinal ulceration, bleeding or perforation, with ulcerative colitis or with Crohn's disease, or haematological abnormalities, as these conditions may be exacerbated.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation 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 gastrointestinal 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 systemic corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or antiplatelet agents such as aspirin

When GI bleeding or ulceration occurs in patients receiving aceclofenac, the treatment should be withdrawn.

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.

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

Exceptionally, varicella can trigger serious cutaneous and soft tissues infections complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of Aceclofenac in case of varicella.

Hypersensitivity reactions:

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug.

Haematological:

Aceclofenac Tablets may reversibly inhibit platelet aggregation.

Long-term treatment:

All patients who are receiving NSAIDs should be monitored as a precautionary measure e.g. renal, hepatic function (elevation of liver enzymes may occur) and blood counts.

4.5 Drugs interactions

Trypsin-Chymotrypsin

Herbal Supplements/Alcohol

Systemic proteases may increase the effectiveness of herbal supplements. Chymotrypsin is also known to interact with alcohol.

Antibiotics

Administration of the trypsin-chymotrypsin combination (intramuscularly) has been found to increase the levels of orally administered semi-synthetic penicillin antibiotics in the blood serum and organs of rats.

Chymotrypsin is known to interact with chloramphenicol.

Anticoagulants

The trypsin-chymotrypsin combination should not be administered concurrently with anticoagulants such as coumadin, heparin and clopidogrel.

Paracetamol

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by colestyramine. The anticoagulant effect of warfarin

and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

Aceclofenac

Other analgesics including cyclooxygenase-2 selective inhibitors:

Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects including GI bleeding.

Anti-hypertensives:

NSAIDs, may reduce the effect of activity 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 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.

Diuretics:

Aceclofenac, like other NSAIDs, may inhibit the activity of diuretics. Diuretics can increase the risk of nephrotoxicity of NSAIDs. 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.

Cardiac glycosides like digoxin:

NSAIDs may exacerbate cardiac failure, reduce GFR (glomerular filtration rate) and inhibit the renal clearance of glycosides, resulting in increased plasma glycoside levels. The combination should be avoided unless frequent monitoring of glycoside levels can be performed.

Lithium:

Several NSAID drugs inhibit the renal clearance of lithium, resulting in increased serum concentrations of lithium. The combination should be avoided unless frequent monitoring of lithium can be performed.

Methotrexate:

The possible interaction between NSAIDs and methotrexate should be born in mind also when low doses of methotrexate are used, especially in patients with decreased renal function. When combination therapy has to be used, the renal function should be monitored. Caution should be exercised if both an NSAID 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 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Corticosteroids:

Increased risk of gastrointestinal ulceration or bleeding.

Anti-coagulants:

NSAIDs may enhance the effects of anti-coagulants, such as warfarin. Close monitoring of patients on combined anti-coagulants and Aceclofenac Tablets therapy should be undertaken.

Quinolone antibiotics:

Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs):

Increased risk of gastrointestinal bleeding.

Ciclosporin, Tacrolimus:

Administration of NSAID drugs together with ciclosporin or tacrolimus is thought to increase the risk of nephrotoxicity due to decreased synthesis of prostacyclin in the kidney. During combination therapy it is therefore important to carefully monitor renal function.

Zidovudine:

Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There are indications of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Antidiabetic agents:

Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents with influencing their clinical effect. However, there have been isolated reports of hypoglycaemic and hyperglycaemic effects. Thus with Aceclofenac Tablets, consideration should be given to adjustment of the dosage of hypoglycaemic agents.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Trypsin-Chymotrypsin

Pregnancy

Not enough is known about the use of trypsin and chymotrypsin during pregnancy.

Lactation

Not enough is known about the use of trypsin and chymotrypsin during breastfeeding.

Paracetamol

Pregnancy

In reported epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy if clinically needed, however, as with any medicine it should be used at the lowest effective dose for the shortest possible time.

Breast-feeding

Paracetamol is excreted in breast milk but not in a clinically significant amount in recommended dosages. Available published data do not contraindicate breastfeeding.

Aceclofenac

Pregnancy:

There is no information on the use of Aceclofenac during pregnancy. Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal development. Data from epidemiological studies suggest an increased risk of miscarriage, cardiac malformation or gastroschisis after use of 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. During the first and second trimester of pregnancy, Aceclofenac should not be given unless clearly necessary. If Aceclofenac is used by a women attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

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

- Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

  the mother and the neonate, at the end of pregnancy, to:

- Possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- Inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, aceclofenac is contraindicated during the third trimester of pregnancy

Lactation:

There is no information on the secretion of Aceclofenac to breast milk, there was however no notable transfer of radio labelled (14C) Aceclofenac to the milk of lactating rats.

The use of Aceclofenac Tablets should therefore be avoided in pregnancy and lactation unless the potential benefits to the other outweigh the possible risks to the foetus.

Fertility

The use of Aceclofenac tablets 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 tablets should be considered.

4.7 Effects 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 CHYMORAL-AP. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

Trypsin-Chymotrypsin

Rarely, chymotrypsin might cause an allergic reaction when taken by mouth.Symptoms include itching, shortness of breath, swelling of the lips or throat, shock, loss of consciousness, and death.

Occasional gastric disturbance may also occur.

Paracetamol

Adverse events of paracetamol from historical clinical trial data are both infrequent and from small patient exposure. Accordingly, events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by system class and frequency.

The following convention has been utilised for the classification of the undesirable effects: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000), not known (cannot be estimated from available data).

Adverse event frequencies have been estimated from spontaneous reports received through post-marketing data.

Organ Class	**Undesirable effect**	**Frequency**
Blood and lymphatic system disorders	Thrombocytopenia Agranulocytosis	Very rare
Immune system disorders	Anaphylaxis Cutaneous hypersensitivity reactions including, among others, skin rashes and angioedema. Very rare cases of serious skin reactions have been reported.	Very rare

Respiratory, thoracic and mediastinal disorders	Bronchospasm*	Very rare
Hepatobiliary disorders	Hepatic dysfunction	Very rare

* There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs.

Aceclofenac

Gastrointestinal:

The most commonly-observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease 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 reactions and anaphylaxis (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angiodema and, more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Cardiovascular and cerebrovascular:

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.

Aceclofenac is both structurally related and metabolised to diclofenac for which a greater amount of clinical trial and epidemiological data consistently point towards an increased risk of general arterial thrombotic events (for example myocardial infarction or stroke , particularly at high doses or in long treatment). Epidemiological data has also found an increased risk of acute coronary syndrome and myocardial infarction associated with the use of aceclofenac.

Exceptionally, occurrence of serious cutaneous and soft tissues infections complications during varicella has been reported in association with NSAID treatment.

Other adverse reactions reported less commonly include:

Renal:

interstitial nephritis

Neurological and special senses:

optic neuritis, 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 (confusion, hallucinations, malaise, and drowsiness.

Haematological:

agranulocytosis, aplastic anaemia

Dermatological:

Bullous reactions including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis (very rare). Photosensitivity.

If serious adverse reactions occur, Aceclofenac tablets should be withdrawn.

The following is a table of adverse reactions reported during clinical studies and after authorisation, grouped by System OrganClass and estimated frequencies. Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to<1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Rare ≥1/10,000 to <1/1,000	Anaemia
	Very rare <1/10,000	Bone Marrow depression, Granulocytopenia Thrombocytopenia Neutropenia Haemolytic anaemia
Immune system disorders	Rare ≥1/10,000 to <1/1,000	Anaphylactic reaction (including shock) Hypersensitivity
Metabolism and nutrition disorders	Very rare <1/10,000	Hyperkalemia
Psychiatric disorders	Very rare <1/10,000	Depression Abnormal dreams Insomnia
Nervous system disorders	Common 1/100 to <1/10	Dizziness
	Very rare <1/10,000	Paraesthesia Tremor Somnolence Headache Dysgeusia (abnormal taste)
Eye disorders	Rare ≥1/10,000 to <1/1,000	Visual disturbance
Ear and labyrinth disorders	Very rare <1/10,000	Vertigo Tinnitus
Cardiac disorders	Rare ≥1/10,000 to <1/1,000	Cardiac failure
	Very rare <1/10,000	Palpitations
Vascular disorders	Rare ≥1/10,000 to <1/1,000	Hypertension

	Very rare <1/10,000	Flushing Hot flush vasculitis
Respiratory, thoracic and mediastinal disorders	Rare ≥1/10,000 to <1/1,000	Dyspnoea
	Very rare <1/10,000	Bronchospasm Stridor
Gastrointestinal disorders	Common 1/100 to <1/10	Dyspepsia Abdominal pain Nausea Diarrhoea
	Uncommon ≥1/1,000 to <1/100	Flatulence Gastritis Constipation Vomiting Mouth ulceration
	Rare ≥1/10,000 to <1/1,000	Melaena Gastrointestinal haemorrhage Gastrointestinal ulceration
	Very rare <1/10,000	Stomatitis Intestinal perforation Exacerbation of Crohn's disease and colitis Ulcerative Haematemesis Pancreatitis
Hepatobiliary disorders	Common 1/100 to <1/10	Hepatic enzyme increased
	Very rare <1/10,000	Hepatic injury (including hepatitis) Jaundice Blood alkaline phosphatase increased
Skin and subcutaneous tissue disorders	Uncommon ≥1/1,000 to <1/100	Pruritus Rash Dermatitis Urticaria
	Rare ≥1/10,000 to <1/1,000	Angioedema
	Very rare <1/10,000	Purpura Severe mucocutaneous skin reaction (including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis)
Renal and urinary disorders	Uncommon ≥1/1,000 to <1/100	Blood urea increased Blood creatinine increased

	Very rare <1/10,000	Renal failure Nephrotic syndrome
General disorders and administration site conditions	Very rare <1/10,000	Oedema Fatigue Cramps in legs
Investigations	Very rare <1/10,000	Weight increase

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:
http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

4.9 Overdose

Trypsin-Chymotrypsin

No data available.

Paracetamol

Paracetamol overdose may cause liver failure which may require liver transplant or lead to death.

Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has risk factors.

Risk factors

If the patient:

(a) Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St. John's Wort or other drugs that induce liver enzymes.

or

(b) Regularly consumes ethanol in excess of recommended amounts.

or

(c) Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms

Symptoms of paracetamol overdosage 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, haemorrhage, hypoglycaemia, cerebral oedema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines.

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 may be used up to 24 hours after ingestion of paracetamol, however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous Nacetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital. Management of patients who present with serious hepatic dysfunction beyond 24h from ingestion should be discussed with the NPIS or a liver unit.

Aceclofenac

Symptoms

Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal irritation, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, hypotension, respiratory depression, fainting, occasionally convulsions. In cases of significant poisoning acute renal failure and liver damage are possible.

Therapeutic measure

Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.

Specific therapies such as, dialysis or haemoperfusion are probable of no help in eliminating NSAIDs due to their high rate of protein binding and extensive metabolism. Good urine output should be ensured.

Renal and liver function should be closely monitored. Patients should be observed for at least four hours after ingestion of potentially toxic amounts. In case of frequent or prolonged convulsions, patients should be treated with intravenous diazepam. Other measures may be indicated by the patient's clinical condition.

Management of acute poisoning with oral aceclofenac essentially consists of supportive and symptomatic measuresfor complications such as hypotension, renal failure, convulsions, gastro-intestinal irritation, and respiratory depression.

5. Pharmacological properties

5.1 Mechanism of Action

Trypsin-Chymotrypsin

The cells in the pancreas synthesize and produce digestive enzymes that breakdown fats (lipases), starches (amylases) and proteins (proteases). Pancreatic proteases can be divided

into several families of enzymes that differ in structure and catalytic effect in how they interact with the peptide bonds of proteins. Trypsin and chymotrypsin are two types of proteases originally synthesized in the pancreas in the inactive form of zymogen precursors (trypsinogen and chymotrypsinogen) for the purpose of stopping unnecessary cellular activity and controlling when and where enzyme activity occurs. Zymogens are then carried either into the bloodstream or the intestines where they are excreted or are converted by the process of proteolysis into the active enzymes that aid digestion. When taking the trypsin-chymotrypsin combination, the active proteolytic enzymes are being ingested and used in addition to the inactive forms the body naturally produces. Trypsin and chymotrypsin give the body the extra boost it might need for smoother digestion of proteins as well as for reducing inflammation and fighting infection.

Paracetamol

Paracetamol produces analgesic and antipyretic as main effects and it has been also reported that paracetamol has a weak anti-inflammatory effect. Analgesic action: The central analgesic action of Paracetamol resembles that of aspirin. It produces analgesia by raising pain threshold. Antipyretic effect: The antipyretic effect of Paracetamol is attributed to its ability to inhibit COX in the brain where peroxide tone is low.

Recent evidence suggests inhibition of COX-3 (believed to be splice variant product of the COX-1 gene) could represent a primary central mechanism by which Paracetamol decreases pain and possibly fever. Paracetamol is a peripherally acting analgesic with antipyretic activity.

Aceclofenac

The mode of action of aceclofenac is largely based on the inhibition to prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclo-oxygenase, which is involved in the production of prostaglandins.

5.2 Pharmacodynamic properties

Trypsin-Chymotrypsin

Combination of Trypsin-Chymotrypsin enzyme consist of purified proteolytic enzyme concentrate providing 50,000 armour units of Trypsin and Chymotrypsin activity in the ratio 6.1. It is essential to use a combination of both enzymes because trypsin hydrolysis peptide linkage involving the carboxyl group of agrinine and lysine whereas Chymotrypsin acts on peptide linkages involving phenylalanine, tyrosine and tryptophan.

Therefore complete proteolytic spectrum is achieved only with the combination of Trypsin and Chymotrypsin.

The anti-inflammatory properties in the following ways.

Fibrinolytic activity:

When fibrin clots have stopped bleeding, body's own fibrinolytic agent – plasmin breaks the fibrin barrier. Liver, in response to trauma, releases APR's (Acute Phase Reactants) that inhibits Plasmin (and its fibrinolytic action). Chymotrypsin and trypsin together breaks down the fibrin barrier thus improving and restoring circulation, resolving edema, hematoma and pain, promoting phagocytosis to remove the debris an accelerate recovery.

There are reports suggesting that chymotrypsin trypsin combination helps modulate the process of inflammation. Thus, trypsin and chymotrypsin combination reduces the proinflammatory mediators and fastens the healing process.

The protein bound fraction of the drug exerts a direct fibrinolytic activity at the site of inflammation thus improving microcirculation and dispersion of tissue fluid.

Reduction in Plasmin Inhibitor levels:

In reported studies have been done measure the levels of plasma inhibitors post-surgery with and without the postoperative administration of trypsin - chymotrypsin enzyme. It was found that there was a reversal in the initial rise of plasma inhibitors during the three-to-five day post-operative period as compared to that in the placebo group where these levels were maintained over a longer period. This action is seen because the plasmin inhibitors (alpha 1 antitrypsin and alpha 2 macroglobulin) have greater propensity to bind elastase and cathepsins as compared to Trypsin Chymotrypsin but more affinity to bind Tryosin-Chymotrypsin as compared to plasma to plasmin. Therefore the inhibition of damaging phagocytic proteases by elastases and cathepsins continues while the plasmin inhibiting action is prevented.

Release of Intestinal Plasminogen activators:

Studies have shown that Trypsin-Chymotrypsin brings about release of Plasminogen activators from the intestinal mucosa. Those are absorbed into the systemic circulation along with Trypsin-Chymotrypsin and contribute further to bringing about fibrinolysis. Therefore Trypsin–Chymotrypsin enhances fibrinolysis by a triple mechanism, thereby increasing tissue circulation and decreasing edema.

Increased Microcirculation:

This not only reduces tissue edema but also decreases the contact time of damaged tissue with various inflammatory mediators like leucocytes, immunoglobulins and Plasma complement factors etc.

Smoothens process of digestion:

Trypsin helps to break down large protein molecules by cutting protein chains at specific sites. The large protein molecule is actually a chain of smaller units called amino acids which are linked, end to end, in chains hundreds. There are 20 different amino acids from which these protein chains are made. The specific site along the protein chain where trypsin is active is one with the amino acids lysine and arginine, two of the smaller amino acids.

The enzyme chymotrypsin also cuts the larger protein chain but at different sites from where trypsin cuts. Chymotrypsin makes its cut at positions along the protein chain that contain very large amino acids such as phenylalanine, tyrosine and tryptophan. Otherwise, it is very similar to trypsin.

In some individuals, the production of these digestive enzymes is deficient, resulting in the inability to completely digest food. This can result in abdominal pain, indigestion, gas and malnutrition. This condition is treatable with trypsin chymotrypsin enzyme supplements.

Paracetamol

Paracetamol is an antipyretic analgesic. The mechanism of action is probably similar to that of aspirin and dependant on the inhibition of prostaglandin synthesis. This inhibition appears, however to be on a selective basis.

Clinical Efficacy

In two dental pain reported studies, pain relief was observed at a median time of 15 minutes following administration of the 1000 mg dose of Paracetamol tablets.

Paracetamol tablets demonstrated superior pain relief at 1000 mg dose compared to placebo and to Paracetamol tablets at 500 mg dose. Paracetamol tablets 500 mg dose also demonstrated superior efficacy compared to placebo.

Aceclofenac

Aceclofenac is a non-steroidal agent with marked anti-inflammatory and analgesic properties.

ATC code: M01A B16

The mode of action of aceclofenac is largely based on the inhibition to prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclo-oxygenase, which is involved in the production of prostaglandins.

5.3 Pharmacokinetic properties

Trypsin-Chymotrypsin

Trypsin and Chymotrypsin are related and absorbed in the small intestines. This mode of administration protects the enzymes from being destroyed by acids or other enzymes in the stomach and promotes intestinal absorption. Higher the dosage, higher is the plasma peak levels, but whatever may be the dosage, plasma peak levels are reached in 2-3 hours and return to base level in 8 hours. Therefore the dosage should be repeated every 6 hours. Proof of absorption is provided by the fact that when [13]labeled Trypsin or Chymotrypsin is administered to animals, radioactivity can be detected in plasma. In human volunteers, active esterase levels have been found in the plasma after administration of Trypsin and Chymotrypsin, maximum esterase levels are proportional to the dosage used. Rapid and significant elevation of blood esterase levels are obtained following oral administration.

Paracetamol

Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. The concentration in plasma reaches a peak in 30 to 60 minutes and the plasma half-life is 1 - 4 hours after therapeutic doses.

Paracetamol is relatively uniformly distributed throughout most body fluids. Binding of the drug to plasma proteins is variable; 20 to 30% may be bound at the concentrations encountered during acute intoxication. Following therapeutic doses 90 - 100% of the drug may be recovered in the urine within the first day. However, practically no paracetamol is excreted unchanged and the bulk is excreted after hepatic conjugation.

Paracetamol Tablets contain a disintegrant system which accelerates tablet dissolution compared to standard paracetamol tablets.

Human scintigraphy data demonstrate that Paracetamol tablets generally start to disintegrate by 5 minutes post dose in the stomach. There is also less between-subject and less within-subject variability ($p<0.0001$) in early absorption of paracetamol from paracetamol 500 mg Tablets compared to standard paracetamol tablets.

Human pharmacokinetic data demonstrate that the time taken to reach plasma paracetamol therapeutic threshold (4-7mcg/ml) is at least 37% faster with Paracetamol 500 mg Tablets compared to standard paracetamol tablets ($P<0.05$).

Total extent of absorption of paracetamol from Paracetamol 500 mg Tablets is equivalent to that from standard paracetamol tablets.

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 L.

The mean plasma elimination half-life is around 4 hours. Aceclofenac is highly protein-bound (>99%). Aceclofenac circulates mainly as unchanged drug. 4'- hydroxyaceclofenac is the main metabolite detected in plasma. 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.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Trypsin-Chymotrypsin

No data available

Paracetamol

In reported conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

Aceclofenac

The results from reported preclinical studies conducted with aceclofenac are consistent with those expected for NSAIDs. The principal target organ was the gastro-intestinal tract. No unexpected findings were recorded.

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

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

In reported 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.

7. Description

Trypsin

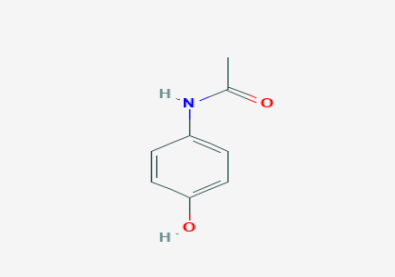
A proteolytic enzyme crystallised from an extract of the pancreas of healthy bovine or porcine animals, or both. It contains not less than 2500 USP units in each mg, calculated on the dried basis. A white to yellowish-white, odourless, crystalline or amorphous powder. Store in airtight containers at temperature not exceeding 40°C.

Chymotrypsin

A proteolytic enzyme crystallised from an extract of the pancreas gland of the ox, Bos taurus (Bovidae). It contains not less than 1000 USP units in each mg, calculated on the dried basis. A white to yellowish-white, crystalline or amorphous, odourless powder. An amount equivalent to 100 000 USP units is soluble in 10 mL of water and in 10 mL of sodium chloride 0.9%. Store in airtight containers at a temperature not exceeding 40°C.

Paracetamol

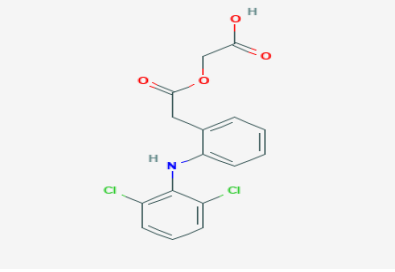
Paracetamol is 4-hydroxyacetanilide having molecular formula of $C_8H_9NO_2$ and molecular weight is 151.2 and the chemical structure is:



Paracetamol is white crystals or white, crystalline powder which is freely soluble in ethanol (95%) and in acetone; sparingly soluble in water; very slightly soluble in dichloromethane and in ether.

Aceclofenac

Aceclofenac is 2-[(2,6-dichlorophenyl)amino]phenylacetoxyacetic acid having empirical formula C16H13Cl2NO4 and molecular weight is 354.2. The chemical structure is:



Aceclofenac is white or almost white, crystalline powder which is freely soluble in acetone; soluble in ethanol (95%); practically insoluble in water.

Trypsin-Chymotrypsin with Paracetamol and Aceclofenac Tablets are yellow coloured, capsule shaped, film coated tablets. The excipients used are Starch, Lactose, PVP-K-30, Methyl Paraben, Propyl Paraben, Seal coat SR 5003, Ethyl Cellulose, Crospovidone, Talcum, Magnesium Stearate, Super Coat (Film) and Titanium Dioxide.

8. Pharmaceutical particulars

8.1 Incompatibilities

None stated

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

CHYMORAL-AP is packed in blister strips of 10 tablets.

8.4 Storage and handing instructions

Store in a cool and dry place. Protect from light. Keep out of reach of children.

9. Patient counselling information

CHYMORAL-AP

Trypsin-Chymotrypsin with Paracetamol and Aceclofenac

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any questions, or if there is anything you do not understand, ask your doctor or pharmacist.
- **This medicine has been prescribed for you only.** Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1 What CHYMORAL-AP is and what it is used for

CHYMORAL-AP is a combination of three active ingredients Trypsin-Chymotrypsin with Paracetamol and Aceclofenac Tablets.

CHYMORAL-AP is used for acute or chronic osteoarthritis, rheumatoid arthritis and spondylo arthritis, spondylosis and other ortho-degenerative disorders, pain management.

9.2 What you need to know before you take CHYMORAL-AP

Do not take CHYMORAL-AP mg Tablets:

- If you have ever had an allergic reaction to trypsin-Chymotrypsin or paracetamol or aceclofenac or to any of the other ingredients
- If you are taking any other prescription or non-prescription medicines containing trypsin-Chymotrypsin or paracetamol or aceclofenac to treat pain, fever, symptoms of cold and flu, or to aid sleep.
- If you have taken aspirin or any other NSAIDs and experienced one of the following:
  - asthma attack causing tightness in the chest wheezing and difficulty breathing.
  - runny nose, itching and/or sneezing (irritation of the nose).
  - raised red circular patchy rash on the skin which may have felt itchy or like a sting or burn.
  - a severe allergic reaction known as anaphylactic shock. The symptoms may be life threatening and include difficulty breathing, wheezing, abdominal pain and vomiting.
- If you have a history of, suffer from, or suspect that you have a stomach ulcer or have vomited blood or passed blood in your faeces (black tarry stools).
- If you have severe kidney disease.
- If 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.
- If you have or have had problems with your blood circulation (peripheral arterial disease).
- If you suffer from, or suspect that you have severe liver failure.
- If you suffer from bleeding or any type of blood clotting disorders.
- If you are pregnant (unless your doctor considers it essential for you to continue to take this medicine)

CHYMORAL-AP is not recommended for use in children.

Ask your doctor before you take this medicine:

- If you suffer from mild arthritis and need to take painkillers every day.
- If you have liver or kidney problems
- If you are underweight or malnourished
- If you regularly drink alcohol
- If you have a severe infection as this may increase the risk of metabolic acidosis.

  Signs of metabolic acidosis include:
  - deep, rapid, difficult breathing

  - feeling sick (nausea), being sick (vomiting)
  - loss of appetite
- If you suffer from any other form of kidney or liver disease.
- If you have any of the following disorders, as they may worsen:
  - Disorders of the stomach or gut/bowel
  - inflammatory bowel disease (ulcerative colitis)
  - chronic inflammatory bowel disease (Crohn's disease)
  - ulceration, bleeding or perforation of the stomach or bowel
- If you have, or have ever had problems with the circulation of the blood to your brain.
- If you suffer from asthma or any other breathing problems.
- If you suffer from a rare inherited disorder known as porphyria.
- If you smoke
- If you have diabetes
- If you have angina, blood clots, high blood pressure, raised cholesterol or other raised body fats such as triglycerides
- If you suffer from an autoimmune condition known as systemic lupus erythematosus or other connective tissue disorders.
- If you are infected with chicken pox, the use of this medicine should be avoided because a rare serious infection of the skin may develop.
- If you are recovering from major surgery.
- If you are elderly (your doctor will prescribe you the lowest effective dose over the shortest duration).

Hypersensitivity reactions can occur and very rarely, very serious allergic reactions are appearing. The risk is higher in the first month of treatment. CHYMORAL-AP should be stopped immediately at the first onset of symptoms such as tightness of the chest, breathing difficulties, fever, skin rashes, soreness of the skin lining the mouth and other mucous membranes causing ulcers, or any signs of hypersensitivity. Medicines such as CHYMORAL-AP may be associated with a small increased risk of heart attack ("myocardial infarction"). Any risk is more likely with high doses and prolonged treatment. Do not exceed the recommended dose or duration of treatment.

Contact a doctor immediately if you get a combination of these symptoms.

You may need to avoid using this product altogether or limit the amount of CHYMORAL-AP that you take.

If you are taking other medicines

Talk to your doctor or pharmacist before taking these tablets if you are taking any prescribed medicines; particularly metoclopramide or domperidone (for nausea [feeling sick] or vomiting [being sick]) or colestyramine (to lower blood cholesterol).

If you take blood thinning drugs (anticoagulants e.g. warfarin) and you need to take a pain reliever on a daily basis, talk to your doctor because of the risk of bleeding. But you can still take occasional doses of CHYMORAL-AP at the same time as anticoagulants.

- medicines used to treat mental health problems like depression (selective serotonin-reuptake inhibitors (SSRIs) such as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) or manic depression (lithium)
- medicines used to treat heart failure and irregular heart beats (cardiac glycosides such as digoxin)
- medicines used to treat high blood pressure (antihypertensives: ACE inhibitors such as enalopril, lisinopril; angiotensin II receptor antagonists such as losartan, candesartan; also hydralazine, methyldopa, clonidine, moxonidine, propranalol)
- medicines to treat infection (quinolone antibiotics such as ciprofloxacin, ofloxacin, levofloxacin moxifloxacin)
- drugs used to increase the rate of urine excretion (diuretics such as thiazides,furosemide amiloride hydrochloride)
- medicines that stop blood clotting (anticoagulants) such as warfarin, heparin
- methotrexate which is used to treat cancer and autoimmune disorders such as arthritis and skin conditions
- mifepristone
- any steroids for the treatment of swelling and inflammation (glucocorticoids such as hydrocortisone, prednisolone,)
- medicines used to suppress the immune system after organ transplant (ciclosporin or tacrolimus)
- medicines used to treat HIV (zidovudine)
- medicines used to lower blood sugar levels in diabetes (antidiabetics such as glibenclamide, glicazide, tolbutamide)
- any other painkiller NSAID drugs (aspirin, ibuprofen, naproxen, COX-2 inhibitors such as celecoxib and etoricoxib)
- antiplatelet drugs such as clopidogrel.

CHYMORAL-AP with food and drink

CHYMORAL-AP must be taken preferably with or after food**.**

Pregnancy and breast feeding

Talk to your healthcare professional before taking CHYMORAL-AP Tablets if you are pregnant.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

The safety of this medicine for use during pregnancy is not known. It is not recommended for use in pregnancy unless considered essential by your doctor. (it must not be used during the last three months of pregnancy).

You should inform your doctor if you have problems becoming pregnant. NSAIDs may make it more difficult to become pregnant.

CHYMORAL-AP should not be used if you are breast-feeding. It is not known if this medicine passes into breast milk. It is not recommended for use during breast-feeding unless considered essential by your doctor.

Driving and using machines:

If you are taking CHYMORAL-AP and you experience dizziness, drowsiness, vertigo, tiredness or any difficulty with your eyesight, you must not drive or use machinery.

9.3 How to take CHYMORAL-AP

Always take this medicine exactly as your doctor or pharmacist has told you.

Method and route of administration:

Swallow the tablet whole with a glass of water. Do not crush or chew the tablets.

Never change the dose of your medicine without talking to your doctor first. Continue to take your tablets for as long as your doctor recommends.

If you take more CHYMORAL-AP Tablets than you should

If you accidentally take too many CHYMORAL-AP Tablets, contact your doctor immediately or go to your nearest hospital casualty department.

Please take this leaflet or the box the CHYMORAL-AP Tablets came in, with you to the hospital so that they will know what you have taken.

If you forget to take CHYMORAL-AP Tablets

If you miss a dose, do not worry, just take the next dose at the usual times. Do not take a double dose to make up for a forgotten dose.

If you stop taking CHYMORAL-AP Tablets

Do not stop taking CHYMORAL-AP Tablets unless your doctor advise you. If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

9.4 Possible side effects

Like all medicines, CHYMORAL-AP Tablets can have side effects but not everybody gets them. A small number of people have had side effects. Very rare cases of serious skin reactions have been reported.

Stop taking the medicine and tell your doctor immediately if you experience:

- Allergic reactions which may be severe such as skin rash and itching sometimes with swelling of the mouth or face or shortness of breath
- Skin rash or peeling, or mouth ulcers
- Breathing problems. These are more likely if you have experienced them before when taking other painkillers such as ibuprofen and aspirin
- Unexplained bruising or bleeding.
- Nausea, sudden weight loss, loss of appetite and yellowing of the eyes and skin.
- Severe allergic reaction (anaphylactic shock). Symptoms may develop quickly and can be life threatening if not immediately treated and include fever, difficulty breathing, wheezing, abdominal pain, vomiting, swelling of the face and throat.
- Severe skin rashes such as Stevens - Johnson syndrome and Toxic Epidermal Necrolysis. These are potentially life-threatening and develop quickly forming large blisters and the skin to peel away. The rash can also appear in the mouth, throat or eyes. Fever, headache and aching of the joints usually occur at the same time.
- Meningitis. The symptoms include high fever, headache, vomiting, blotchy red rashes, neck stiffness, sensitivity and intolerance to light.
- passing blood in your faeces (stools/motions).
- passing black tarry stools. Vomit any blood or dark particles that look like coffee grounds.
- kidney failure.

Stop taking the medicine and seek medical advice if you experience:

- indigestion or heartburn
- abdominal pain (pains in your stomach) or other abnormal stomach symptoms.
- blood disorders such as reduced production of blood cells, abnormal breakdown of red blood
- haemolytic anaemia, low content of iron in the blood, low level of white blood

  low number of platelet cells, increased blood potassium levels which can irritate the blood vessels causing inflammation known as vasculitis. These disorders can cause you to feel extremely tired, breathless, aching of the joints and be prone to repeated infections and bruising

If any of the below side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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

- dizziness
- nausea (feeling sick)

- diarrhoea
- increased liver enzymes in the blood

Uncommon (may affect up to 1 in 100 people):

- wind
- inflammation or irritation of the lining of the stomach
- constipation
- vomiting
- mouth ulcers
- itching
- rash
- inflammation of the skin
- raised circular red itchy, stinging or burning patches on the skin (hives)
- increase in blood urea levels
- increase in blood creatinine levels

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

- hypersensitivity (allergic reaction)
- problems with eyesight
- heart failure
- high blood pressure shortness of breath
- bleeding from the stomach or bowel
- stomach or bowel ulceration

Very Rare (may affect up to 1 in 10,000 people):

- depression
- strange dreams
- inability to sleep
- tingling, pricking or numbness of skin
- uncontrollable shaking
- drowsiness
- headaches
- abnormal taste in the mouth
- sensation of spinning when standing still

- ringing in the ears
- heart pounding or racing hot flushes
- difficulty breathing
- high pitched noise when breathing
- inflammation of the mouth
- perforation of either the stomach, large intestine or bowel wall
- worsening of colitis and Crohn's disease
- inflammation of the pancreas injury of the liver (including hepatitis)
- yellowing of the skin (jaundice)
- spontaneous bleeding into the skin (appears as a rash)
- nephrotic syndrome: a condition which indicates kidney damage and includes large amounts of protein in the urine, low blood albumin levels, high blood cholesterol levels and swelling of the legs, feet or ankles
- water retention and swelling
- tiredness
- leg cramps
- increased blood alkaline phosphatase levels
- weight gain

Other side effects that have been reported with this type of drug (NSAIDs) are:

- hallucinations
- confusion
- blurred, partial or complete loss of vision
- painful movement of the eye
- worsening of asthma
- skin reaction to sunlight
- inflammation of the kidneys
- generally feeling unwell

Serious skin infections may occur in association with chickenpox

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting. By reporting side effects, you can help provide more information on the safety of this medicine

9.5 How to store CHYMORAL-AP

Store in a cool and dry place. Protect from light.

9.6 Contents of the pack and other information

What **CHYMORAL-AP** contains

The active substances **CHYMORAL-AP** is Trypsin-Chymotrypsin with Paracetamol and Aceclofenac.

The excipients used are Starch, Lactose, PVP-K-30, Methyl Paraben, Propyl Paraben, Seal coat SR 5003, Ethyl Cellulose, Crospovidone, Talcum, Magnesium Stearate, Super Coat (Film) and Titanium Dioxide.

10. Details of manufacturer

Manufactured in India by:

Synokem Pharmaceuticals Ltd.

Plot No. 56-57, Sector-6A, IIE, (SIDCUL), Ranipur (BHEL), Haridwar – 249403, (Uttarakhand).

11. Details of permission or licence number with date

Mfg. Lic. No. : 27/UA/SC/P-2018 issued on 06.02.2016.

12. Date of revision

AUG/2020

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/CHYMORAL-AP 325/100 mg/AUG-20/03/PI