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

CHYMORAL PLUS

1. Generic Name

Trypsin-Chymotrypsin with Diclofenac Potassium Tablets

2. Qualitative and quantitative composition

Each sugar-coated tablet contains:

50,000 Armour Units of Enzymatic Activity*

*Supplied by a Purified Concentrate which has Specific Trypsin and Chymotrypsin Activity in a Ratio of Approximately Six to One

(In enteric coated form)

Diclofenac Potassium I.P. ..... 50 mg

Colour: Titanium Dioxide I.P.

The List of Excipients are Polyethylene Glycol, Sorbitol, Mannitol, Isopropyl Alcohol, Acetone, Methacrylic acid Copolymer, Magnesium stearate, Glycerol Mono-oleate, Ethyl Cellulose, Talc, Gelatin, Sucrose, Gum Acacia, Calcium Carbonate, Polyvinyl Pyrrolidone, Sodium Carboxy Methyl Cellulose, Polysorbate, Titanium Dioxide, Colloidal Silicon Dioxide, Carnauba Wax.

3. Dosage form and strength

Dosage form: Sugar-coated tablet

Dosage Strength: Trypsin-Chymotrypsin 50,000 Armour Units and Diclofenac Potassium 50 mg

4. Clinical particulars

4.1 Therapeutic indication

It is indicated for the treatment of mild acute edematous inflammatory painful conditions.

4.2 Posology and method of administration

Posology

The dose and dose frequency of Chymoral Plus will be decided under the supervision of qualified physician.

Method of administration

As directed by the Physician.

4.3 Contraindications

Trypsin-Chymotrypsin

- Adjunctive therapy in management of inflammatory edema due to injury, surgery, infection or dental procedures
- Hypersensitivity to Chymoral ingredients or enzymes
- Chymoral is contraindicated in patients with severe liver, kidney impairment, peptic ulcer, high vitreous pressure, and hypersensitivity.

Diclofenac

- Hypersensitivity to the active substance or any of the excipients.

- Active, gastric or intestinal ulcer, bleeding or perforation.
- History of gastrointestinal bleeding or perforation, relating to previous NSAID therapy Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
- Last trimester of pregnancy
- Hepatic failure
- Renal failure
- Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac is also contraindicated in patients in whom attacks of asthma, angioedema, urticaria or acute rhinitis are precipitated by ibuprofen, acetylsalicylic acid or other nonsteroidal anti- inflammatory drugs.

4.4 Special warnings and precautions for use

Trypsin-Chymotrypsin

Chymotrypsin is safe when used in the eye by a healthcare professional. It can cause side effects when used in the eye, including an increase in pressure in the eye and other eye conditions such as uveitis, paralysis of the iris, and keratitis.

Chymotrypsin also seems to be safe for most people when taken by mouth to reduce redness and swelling following surgery or injury, and when applied directly to the skin for burns.

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 be employed in patients with severe hepatic insufficiency or renal damage or irregularities of blood clotting mechanism.

Trypsin and Chymotrypsin should not be employed in patients with severe hepatic insufficiency and should be given cautiously to patient with renal damage or irregularities of blood clotting mechanism. It should be used for a week after pulmonary hemorrhage.

After many years of widespread clinical use, there is no reason to believe that Trypsin and Chymotrypsin is, or may be teratogenic in humans. However, its sound medical principle to exercise precaution in prescribing any medications during the first three months of pregnancy.

Severe hepatic or renal disease. To be used with caution during Lactation, or in the elderly, children, pregnancy (use only, if clearly indicated) and patients with irregularities of blood clotting mechanism.

Diclofenac

General

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

The concomitant use of Diclofenac with systemic NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects.

Caution is indicated in the elderly on basic medical grounds. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight.

As with other nonsteroidal anti-inflammatory drugs including diclofenac, allergic reactions,

including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug. Like other NSAIDs, diclofenac may mask the signs and symptoms of the infection due to its pharmacodynamic properties.

Gastrointestinal effects:

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

As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be excised when prescribing diclofenac in patients with symptoms indicative of gastrointestinal disorders, or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation. The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses including diclofenac, and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation.

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

To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly, the treatment should be initiated and maintained at the lowest effective dose.

Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant use of medicinal products containing low dose acetylsalicylic acid (ASA/aspirin or medicinal products likely to increase gastrointestinal risk.

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding).

Caution is recommended 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 (SSRIs) or anti-platelet agents such as acetylsalicylic acid.

Close medical surveillance and caution should be exercised in patients with ulcerative colitis, or with Crohn's disease as these conditions may be exacerbated.

Hepatic effects:

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

As with other NSAIDs, including diclofenac, values of one or more liver enzymes may increase. During prolonged treatment with diclofenac, regular monitoring of hepatic function is indicated as a precautionary measure.

If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), diclofenac should be discontinued.

Hepatitis may occur with diclofenac without prodromal symptoms.

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

Renal effects:

As fluid retention and oedema have been reported in association with NSAIDs therapy, including

diclofenac, particular caution is called for in patients with impaired cardiac or renal function, history of hypertension, the elderly, patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery. Monitoring of renal function is recommended as a precautionary measure when using diclofenac in such cases. Discontinuation therapy is usually followed by recovery to the pre-treatment state.

Skin effects:

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens- Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs, including diclofenac. Patients appear to be at the 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. Diclofenac should be discontinued at the first appearance of skin rash, mucosal lesions or any other signs of hypersensitivity.

SLE and mixed connective tissue disease:

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis.

Cardiovascular and cerebrovascular effects:

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

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy, including diclofenac.

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

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with diclofenac after careful consideration.

Hematological effects:

Use of diclofenac are recommended only for short term treatment.

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

Diclofenac may reversibly inhibit platelet aggregation. Patients with defects of hemostasis, bleeding diathesis or hematological abnormalities should be carefully monitored.

Pre-existing asthma:

In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions on NSAIDs like asthma exacerbations (so called intolerance to analgesics / analgesics asthma), Quincke's oedema or urticaria are more frequent than in other patients. Therefore, special precaution is recommended in such patients (readiness for emergency). This is applicable as well for patients who are allergic to other substances, e.g. with skin reactions, pruritus or urticaria.

Like other drugs that inhibit prostaglandin synthetase activity, diclofenac sodium and other NSAIDs can precipitate bronchospasm if administered to patients suffering from, or with a previous history of bronchial asthma.

Female fertility:

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

4.5 Drugs interactions

Trypsin-Chymotrypsin

When certain medications are taken together with Trypsin drug interactions could occur that may affect the efficacy of the medicines. It can even increase your risk for side effects. Trypsin can interact with other medicines such as vitamins, minerals, herbal products, and drugs prescribed by other doctors resulting in side effects or altered effectiveness of Trypsin.

Drug- drug interactions :

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

Antibiotics

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

Chymotrypsin is known to interact with chloramphenicol.

Anticoagulants

Trypsin chymotrypsin combination should not be administered concurrently with anticoagulants such as Coumadin, Heparin and clopidogrel.

Diclofenac

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

Lithium: If used concomitantly, diclofenac may increase plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.

Digoxin: If used concomitantly, diclofenac may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

Diuretics and antihypertensive agents: Like other NSAIDs, concomitant use of diclofenac with diuretics and antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis.

Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated, and consideration should be given to monitoring of renal function after initiation of concomitant therapy periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity.

Drugs known to cause hyperkalemia: Concomitant treatment with potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should therefore be monitored frequently.

Anticoagulants and anti-platelet agents: Caution is recommended since concomitant administration could increase the risk of bleeding. Although clinical investigations do not appear to indicate that diclofenac has an influence on the effect of anticoagulants, there are reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulant concomitantly. Therefore, to be certain that no change in anticoagulant dosage is required, close monitoring of such patients is required. As with other nonsteroidal anti-inflammatory agents, diclofenac in a high dose can reversibly inhibit platelet aggregation.

Other NSAIDs including cyclooxygenase-2 selective inhibitors and corticosteroids: Co-administration of diclofenac with other systemic NSAIDs or corticosteroids may increase the risk of gastrointestinal bleeding or ulceration. Avoid concomitant use of two or more NSAIDs.

Selective serotonin reuptake inhibitors (SSRIs): Concomitant administration of SSRI's may increase the risk of gastrointestinal bleeding.

Antidiabetics: Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

Methotrexate: Diclofenac can inhibit the tubular renal clearance of methotrexate hereby increasing methotrexate levels. Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increase. Cases of serious toxicity have been reported when methotrexate and NSAIDs, including diclofenac are given within 24 hours of each other. This interaction is mediated through accumulation of methotrexate resulting from impairment of renal excretion in the presence of the NSAID.

Ciclosporin: Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin due to the effect on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus. This might be mediated through renal antiprostaglandin effects of both NSAID and calcineurin inhibitor.

Quinolone antibacterials: Convulsions may occur due to an interaction between quinolones and NSAIDs. This may occur in patients with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving an NSAID.

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

Colestipol and cholestyramine: These agents can induce a delay or decrease in absorption of diclofenac. Therefore, it is recommended to administer diclofenac at least one hour before or 4 to 6 hours after administration of colestipol/ cholestyramine.

Cardiac glycosides: Concomitant use of cardiac glycosides and NSAIDs in patients may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

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

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

4.6 Use in special population (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. Stay on the safe side and avoid use.

Lactation

Not enough is known about the use of trypsin and chymotrypsin during breastfeeding. Stay on the safe side and avoid use.

Diclofenac

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and or cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1% up to approximately 1.5%.

The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has 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 organogenetic period. If diclofenac is used by a woman attempting to conceive, or during the 1st 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 the 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, diclofenac is contraindicated during the third trimester of pregnancy.

Lactation

Like other NSAIDs, diclofenac passes into breast milk in small amounts. Therefore diclofenac should not be administered during breast feeding in order to avoid undesirable effects in the infant.

Female fertility

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

4.7 Effects on ability to drive and use machines

Diclofenac

Patients who experience visual disturbances, dizziness, vertigo, somnolence, central nervous system disturbances, drowsiness, or fatigue while taking NSAIDs should refrain from driving or operating machinery.

4.8 Undesirable effects:

Trypsin-Chymotrypsin

Hepatic damage and necrosis may precipitate arrhythmias, shivering during recovery. 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.

Diclofenac

Adverse reactions are ranked under the heading of frequency, the most frequent first, using the following convention: very common: (>1/10); common (≥ 1/100, <1/10); uncommon (≥ 1/1,000, <1/100); rare (≥1/10,000, <1/1000); very rare (<1/10,000); not known: cannot be estimated from available data.

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

Table 1

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

Unknown	Optic neuritis.
Ear and labyrinth disorders	
Common	Vertigo
Very rare	Tinnitus, hearing impaired
Cardiac disorders	
Uncommon*	Myocardial infarction, cardiac failure, palpitations, chest pain.
Vascular disorders	
Very rare	Hypertension, hypotension, vasculitis.
Respiratory, thoracic and mediastinal disorders	
Rare	Asthma (including dyspnoea).
Very rare	Pneumonitis
Gastrointestinal disorders	
Common	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia.
Rare	Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer with or without bleeding or perforation (sometimes fatal particularly in the elderly).
Very rare	Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis.
Unknown	Ischaemic colitis
Hepatobiliary disorders	
Common	Transaminases increased.
Rare	Hepatitis, jaundice, liver disorder
Very rare	Fulminant hepatitis, hepatic necrosis, hepatic failure.
Skin and subcutaneous tissue disorders	
Common	Rash
Rare	Urticaria

Very rare	Bullous eruptions, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura, allergic purpura, pruritus.
Renal and urinary disorders	
Very rare	Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis.
Reproductive system and breast disorders	
Very rare	Impotence
General disorders and administration site conditions	
Rare	Oedema

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com.

4.9 Overdose

Trypsin-Chymotrypsin

No data available.

Diclofenac

Symptoms

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

Therapeutic measures

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

Special measures such as forced diuresis, dialysis or haemo-perfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to high protein binding and extensive metabolism.

Activated charcoal may be considered after ingestion of a potentially toxic overdose, and gastric decontamination (e.g. vomiting, gastric lavage) after ingestion of a potentially life threatening overdose.

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.

Diclofenac

Diclofenac is a non-steroidal agent with marked analgesic/anti-inflammatory properties. It is an inhibitor of prostaglandin synthetase, (cyclo-oxygenase).

Diclofenac *in vitro* does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in human beings.

5.2 Pharmacodynamic properties

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 blood stream or the intestines where they are excreted or are converted by process of proteolysis into the active enzymes that aid digestion. When taking 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 reducing inflammation and fighting infection.

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 arginine 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 break 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:

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 Tyrosin- 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.

Diclofenac

Pharmacotherapeutic group: Nonsteroidal anti-inflammatory drug (NSAID).

Chymoral Plus tablets contain the potassium salt of diclofenac, a nonsteroidal compound with pronounced and clinically demonstrable analgesic, anti-inflammatory and anti-pyretic properties.

Diclofenac is a potent inhibitor of prostaglandin biosynthesis and modulator of arachidonic acid release and uptake.

Diclofenac has a rapid onset of action and are therefore suitable for the treatment of acute episodes of pain and inflammation.

In migraine attacks diclofenac has been shown to be effective in relieving the headache and in improving the accompanying symptom of nausea.

Diclofenac in vitro does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in human beings.

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 labelled Trypsin or Chymotrypsin is administered to animals; radioactivity can be detected in plasma. Inhuman 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.

Diclofenac

Absorption:

Diclofenac is rapidly and completely absorbed from sugar-coated tablets. Food intake does not affect absorption.

Peak plasma concentration after one 50 mg sugar-coated tablet was 3.9 µmol/l after 20-60 minutes. The plasma concentrations show a linear relationship to the size of the dose.

Diclofenac undergoes first-pass metabolism and is extensively metabolised. Distribution:

Diclofenac is highly bound to plasma proteins (99.7%), chiefly albumin (99.4%). Diclofenac was detected in a low concentration (100 ng/mL) in breast milk in one nursing mother. The estimated amount ingested by an infant consuming breast milk is equivalent to a 0.03 mg/kg/day dose.

Elimination:

The total systemic clearance of diclofenac in plasma is 263 ± 56 ml/min (mean ± SD). The terminal half-life in plasma is 1-2 hours.

Repeated oral administration of diclofenac for 8 days in daily doses of 50 mg t i d does not lead to accumulation of diclofenac in the plasma.

Approx. 60% of the dose administered is excreted in the urine in the form of metabolites, and less than 1% as unchanged substance. The remainder of the dose is eliminated as metabolites through the bile in the faeces.

Biotransformation:

The biotransformation of diclofenac involves partly glucuronidation of the intact molecule, but mainly single and multiple hydroxylation followed by glucuronidation.

Characteristics in patients:

The age of the patient has no influence on the absorption, metabolism, or excretion of diclofenac.

In patients suffering from renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics when applying the usual dosage schedule. At a

creatinine clearance of <10 ml/min the theoretical steady-state plasma levels of metabolites are about four times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile.

In the presence of impaired hepatic function (chronic hepatitis, non-decompensated cirrhosis) the kinetics and metabolism are the same as for patients without liver disease.

6. Nonclinical properties

6.1 Animal Toxicology or pharmacology

Diclofenac

Relevant information on the safety of diclofenac is included in other sections.

7. Description

Trypsin

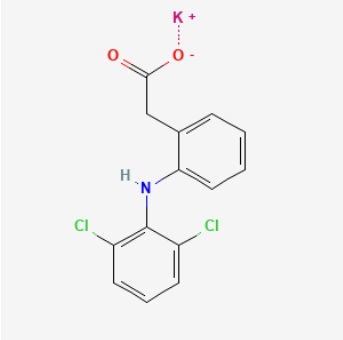
A proteolytic enzyme crystallised from an extract of the pancreas of healthy bovine or porcine animals, or both. It contains not less than 2500 USP units in each mg, calculated on the dried basis. A white to yellowish-white, odourless, crystalline or amorphous powder. Store in airtight containers at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

Diclofenac Potassium

Diclofenac Potassium is potassium 2-[2-(2,6-dichloroanilino)phenyl]acetate. The empirical formula is $C_{14}H_{10}Cl_2KNO_2$ and molecular weight is 334.2 g/mol. The chemical structure is:



Chymoral Plus

Chymoral Plus is white, Circular, biconvex, sugar coated tablets. The List of Excipients are Polyethylene Glycol, Sorbitol, Mannitol, Isoproply Alcohol, Acetone, Methacrylic acid Copolymer, Magnesium stearate, Glycerol Mono-oleate, Ethyl Cellulose, Talc, Gelatin, Sucrose, Gum Acacia, Calcium Carbonate, Polyvinyl Pyrrolidone, Sodium Carboxy Methyl Cellulose, Polysorbate, Titanium Dioxide, Colloidal Silicon Dioxide, Carnauba Wax.

8. Pharmaceutical particulars

8.1 Incompatibilities

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

Chymoral plus is available in pack of 15 tablets.

8.4 Storage and handing instructions

Store in a dry place below 25°C.

Warning: Not for veterinary use.

Keep out of reach of Children

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details Of Manufacturer

Windlas Biotech Limited (Plant-2)

Khasra No.: 141-143 & 145,

Mohabewala Industrial Area,

Dehradun-248 110, Uttarakhand.

11. Details Of Permission Or Licence Number With Date

Mfg. Licence No: 55/UA/SC/P-2013, Issued on: 29.11.2022

12. Date of revision

FEB-2026

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/CHYMORAL PLUS 50mg/Feb-2026/03/PI