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

CHYMORAL – BR

1. Generic Name

Trypsin-Chymotrypsin with Bromelain and Rutoside Trihydrate tablets.

2. Qualitative and quantitative Composition:

CHYMORAL - BR

Each enteric-coated tablet contains:

50,000 Armour Units Enzymatic Activity

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

Bromelain U.S.P. ……...……. 90 mg

Rutoside Trihydrate B.P. …….. 100 mg

Colour: Sunset Yellow.

The excipients used are Starch, Gelatin, Sodium Starch Glycolate, Methyl Paraben, Propyl Paraben, Magnesium Sterate, Talcum, Titanium Dioxide, Sunset Yellow Lake, Isopropyl Alcohol, Acetone, Sucrose, Bees Wax, Wax Carnauba, Sunset Yellow Supra, Celloulose Acetate Phosphate, Dietyl Phthalate.

3. Dosage form and strength

Dosage form: Enteric-Coated Tablet

Strength: 90mg + 100mg+ 50000AU

4. Clinical particulars

4.1. Therapeutic indication

CHYMORAL - BR is used in the treatment of inflammation and Edema of traumatic origin. Major Indications for Chymoral - BR remain severe oedematic and inflammatory conditions such as Traumatic injury, Fractures, Joint Replacement Surgery, Osteoarthritis, Rheumatoid arthritis, Sprain and Hematoma.

4.2. Posology and method of administration

Dosage and Administration

As directed by the Physician.

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

4.3. Contraindications

- 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.

4.4. Special warnings and precautions for use

Chymoral BR must not be used in case of known hypersensitivity to its active ingredients. The preparation must not be used by patients with severe inborn or gained coagulation disorders. (E.g- hemophilia, severe liver damage, dialyzed patients) or with severe hepatic or renal impairment. Proteolytic enzymes can because IgE mediated respiratory allergies of both the immediate type and the late-phase of immediate type. Bromelain is considered a potential ingestive allergen.

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 wide spread clinical use, there is no reason to believe that Trypsin and Chymotrypsin is, or may be teratogenic in humans. However it 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.

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.

Rutoside

Rutoside is contraindicated in individuals who are allergic to plant rutins and O-beta-hydroxyethyl-rutosides containing plants such as rue, buckwheat and tobacco.

4.5. Drugs interactions

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 anti-coagulants such as Coumadin, Heparin and clopidogrel.

Rutoside

Rutoside may interact and exhibits additive effects with horse chestnut extract, Bromelain, N-acetylcysteine, quercetin and buckwheat herb tea.

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

No data available.

4.7. Effects on ability to drive and use machines

No data available.

4.8. Undesirable effects

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.

Chymoral BR is usually well tolerated. A sensation of fullness, flatulence, and occasional episodes of nausea are possible during high- dosage administration. Caution is advised if administering Bromelain to individuals with hypertension, since one report indicated individuals with pre-existing hypertension might experience tachycardia following high doses of Bromelain.

Bromelains may cause nausea, vomiting, and diarrhoea. Metrorrhagia and menorrhagia have occasionally occurred. Hypersensitivity reactions have been reported and have included skin reactions and asthma.

Reporting of adverse reactions

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: https://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.

4.9. Overdose

No data available.

5. Pharmacological properties

5.1. Mechanism of Action

Trypsin, Bromelain and Rutoside combinations control all aspects of inflammatory processes, however proteolytic action of trypsin is incomplete without chymotrypsin, as both work as a pair in sparing plasmin from α- antitrypsin, thus provide a superior fibrinolytic action. Thus

Chymoral BR which combines chymotrypsin with the above combination becomes the most natural choice for Complete & Brisk healing in severe oedematic and inflammatory conditions.

5.2. Pharmacodynamic properties

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 50,000/1,00,000/2,00,000 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:

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.

Bromelain

Bromelains are a concentrate of proteolytic enzymes derived from the pineapple plant, Ananas comosus (A. sativus) (Bromeliaceae). They are used as an adjunct in the treatment of soft tissue inflammation and oedema associated with trauma and surgery.

Bromelains have also been given as an aid to digestion, and used in the treatment of partial deep dermal and full thickness burns.

Bromelain is a crude extract from the pineapple that contains, among other components, various closely related proteinases, demonstrating, in vitro and in vivo, antiedematous, antiinflammatory, antithrombotic and fibrinolytic activities.

Bromelain is used as an anti-inflammatory and analgesic agent in treating the symptoms of arthritis. The analgesic and anti-inflammatory effects are reportedly due to inhibition of the arachidonic acid pathway of inflammation by selectively decreasing thromboxane generation, changing the ratio of thromboxane/prostacyclin (in favor of prostacyclin), and inhibiting PGE2 in addition to the direct effects on the nociceptors. Other reported anti-inflammatory mechanisms of action of bromelain include inhibition of bradykinin at the site of inflammation via depletion of the plasma kallikrein system, and limiting the formation of fibrin by reduction of clotting cascade intermediates. A few clinical trials in patients with arthritis reported statistical equivalence of pain reduction, whether they were treated with bromelain or diclofenac.

Complete Anti-inflammatory Action due to inhibition of various mediators by trypsin and chymotrypsin. Bromelain has potent anti-inflammatory and anti-oedematic action. Chymoral brings about brisk restoration of micro-circulation, reduction of bacterial overload and brisk relief from pain

Rutoside

Rutoside is a natural flavone derivative. It has anti-inflammatory, anti-allergy and immunomodulating activity. Rutoside inhibits platelet aggregation, as well as decreasing capillary permeability, making the blood thinner and improving circulation. Rutin also strengthens the capillaries. It helps to prevent venous edema of the legs. Thus, rutoside is useful in the management of venous edema and capillary fragility. Rutoside is a powerful anti-oxidants and effectively combat the harmful free radicals such as nitric oxide, released during the inflammatory process. Rutoside also suppresses the major inflammatory and proarthritic mediators of macrophages. The ability of Rutoside to decrease MCP-1 levels in vivo and in vitro may add to its beneficial effects because this cytokine is a potent stimulator of monocyte recruitment into the site of inflammation. Rutoside also inhibit the phosphorylation and activation of Jun N-terminal kinase/stress-activated protein kinase, leading to the suppression of AP-1 activation. They also decrease the activation of NF-κB in both human and experimental models.

COMBINATION OF TRYPSIN, RUTOSIDE AND BROMELAIN

Combination of Trypsin, Rutoside and Bromelain has shown to have significant anti-inflammatory effects in several clinical studies. However, the combined mechanism of action of these agents is not clear and need to be explored further.

In a clinical study conducted in 2004, the efficacy of an enzyme-flavonoid mixture was compared with diclofenac, a prescription NSAID.The proteolytic enzymes used were bromelain and trypsin. These three agents were used in the form of an enteric-coated tablet (to prevent the enzymes from being destroyed by stomach acid) that contained 90 mg of bromelain, 48 mg of trypsin, and 100 mg of rutoside. For the 6-week trial, the researchers recruited 103 middle-aged patients who had painful osteoarthritis of the knee with a disease flare in one knee joint. The results showed that diclofenac and the bromelain/trypsin/rutoside mixture were about equally effective in relieving the patients' pain and improving their mobility, with no serious adverse events in either case. In another clinical study conducted in 2006, the Phlogenzym- (PE-fixed dose combination of trypsin, bromelain and rutoside) was compared to the non-steroidal anti-inflammatory drug (NSAID) diclofenac in patients with osteoarthritis of the hip. After six weeks of observation this trial showed significant non-inferiority from 6 weeks treatment with PE in patients with osteoarthritis of the hip and with regard to drug tolerability some tendencies in favour of PE. Thus, PE may well be recommended for the treatment of patients with osteoarthritis of the hip with signs of inflammation as indicated by a high pain level.

5.3. Pharmacokinetic properties

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. 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.

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

No data available.

7. Description

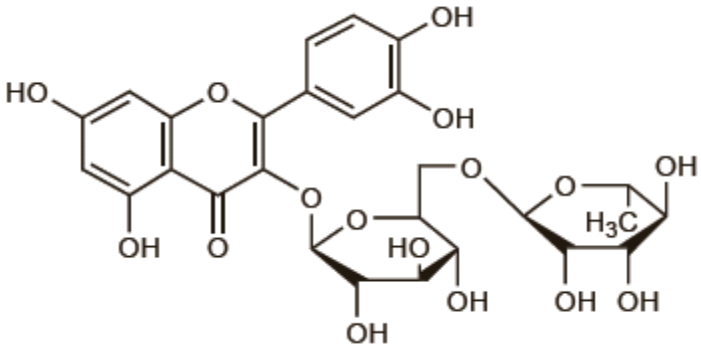
Trypsin, Bromelain and Rutoside combinations control all aspects of inflammatory processes, however proteolytic action of trypsin is incomplete without chymotrypsin, as both work as a pair in sparing plasmin from α- antitrypsin, thus provide a superior fibrinolytic action. Thus Chymoral BR which combines chymotrypsin with the above combination becomes the most natural choice for Complete & Brisk healing in severe oedematic and inflammatory conditions.

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.

Rutoside

Rutoside is a flavonoid obtained from buckwheat, *Fagopyrum esculentum* (Polygonaceae), or from other sources which include the flower buds of the Japanese pagoda-tree, Sophora japonica, and the leaves of several species of *Eucalyptus*.



Chymoral BR is orange coloured, round biconvex, enteric coated tablet The excipients used are Starch, Gelatin, Sodium Starch Glycolate, Methyl Paraben, Propyl Paraben, Magnesium Sterate, Talcum, Titanium Dioxide, Sunset Yellow Lake, Isopropyl Alcohol, Acetone, Sucrose, Bees Wax, Wax Carnauba, Sunset Yellow Supra, Celloulose Acetate Phosphate, Dietyl Phthalate.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

9. Do not use later than date of expiry.

9.1. Packaging information

Chymoral - BR is available in blister pack of 10 tablets.

9.2. Storage and handing instructions

Store below 25°c in a dry place.Protect from light.

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

Synokem Pharmaceuticals Ltd.
Plot No. 35-36, Sector-6A,
Integrated Industrial Estate (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 12.12.2023

12. Date of revision

DEC 2024

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

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