DESCRIPTION

NIMULID-SP is a fixed dose combination (FDC) of Nimesulide and Serratiopeptidase. Nimesulide is chemically 4-Nitro-2-phenoxymethane sulphonanilide and Serratiopeptidase is proteolytic enzyme. Nimulid-SP is grey-yellow, size “2” hard gelatin capsule containing light-yellow coloured granular powder.

COMPOSITION

Each hard gelatin capsule contains:
Nimesulide BP .......... 100mg
Serratiopeptidase ........ 15mg
(equivalent to enzyme activity 30,000 units, as enteric coated granules)

PHARMACOLOGY

The anti-inflammatory, analgesic and antipyretic activities of Nimesulide, a nonsteroidal anti-inflammatory drug (NSAID) of the sulfonanilide class, have been demonstrated in a number of experimental models and in numerous clinical trials.¹

Nimesulide appears to exert its therapeutic effects through a variety of mechanisms viz:²

- Selective cyclooxygenase 2 inhibitor
- Inhibition of generation of superoxide anions from stimulated polymorphonuclear leucocytes.
- Inhibition of platelet activating factor synthesis
- Prevention of Bradykinin/Cytokine induced hyperalgesia of nerves (Inhibiting release of TNF-α)
- Scavenging of hypochlorous acid
- Blocking of histamine release
- Prevention of cartilage damage by inhibition of metalloprotease synthesis
- Phosphodiesterase type IV inhibition.

Serratiopeptidase
Serratiopeptidase is a proteolytic enzyme available for clinical use more than a decade. It binds to alpha-2-macroglobulin in the blood in the ratio of 1:1 which helps to mask its antigenicity but retains its enzymatic activity and is slowly transferred to site of inflammation. Serratiopeptidase hydrolyses bradykinin, histamine and serotonin responsible for oedematic status. It reduces swelling improves microcirculation & expectoration of sputum etc. Thus it can be concluded that serratiopeptidase has anti-inflammatory, anti-oedemic and fibrinolytic activity and acts rapidly on localized inflammation.

**Rationality**

Various painful inflammatory conditions including those associated with osteoarthritis, post operative trauma, sports injuries, bronchitis, sinusitis etc are improved with Nimesulide. Nimesulide is a potent and time tested NSAID and its spectrum of activity is improved by Serratiopeptidase, as Serratiopeptidase exhibits following activities:

1. **Antinflammatory and antiswelling:**
   a. Inhibition of vascular permeability due to scald or injury
   b. Inhibition of inflammatory edema due to carrageenin, serotonin, bradykinin
   c. Excellent decomposability of bradykinin
   d. Strong decomposability of fibrin
   e. No effects of alpha-, beta-globulin and albumin

2. **Action to promote the lysis and discharge of sputum and pus:**
   a. Decreased pus and viscosity in patients with chronic sinusitis.
   b. Decreased sputum and viscosity in patients with subacute bronchitis.

3. **Action to promote transfer of antibiotics to the focal site:**

It can promote the transfer of ampicillin and sulbenicillin to the palate of patients with chronic sinusitis.

Hence, it can be said that Nimesulide and Serratiopeptidase show synergistic potential which is one of the most important factor in deciding the feasibility of a FDC.

**PHARMACOKINETICS**

**Nimesulide**

After oral administration of Nimesulide 50 to 200 mg to healthy adult volunteers, peak serum concentrations of 1.98 to 9.85 mg/L are achieved within 1.22 to 3.17 hours. Oral drug absorption is nearly complete and concomitant administration of food may decrease the rate, but not the extent, of absorption of Nimesulide. The drug is extensively bound (99%) to plasma proteins and has an estimated apparent volume of distribution of 0.19 to 0.35 L/kg following oral administration. Nimesulide is extensively metabolised (1 to 3% of a dose is excreted unchanged in the urine) to several metabolites which are excreted mainly in the urine (≈ 70%) or the faeces (≈ 20%). The drug is almost completely biotransformed into 4-Hydroxy-Nimesulide in both free and conjugated forms and this metabolite appears to contribute to the anti-inflammatory activity of the compound. Peak concentrations of 4-Hydroxy-Nimesulide ranged from 0.84 to 3.03 mg/L and were attained within 2.61 to 5.33 hours after oral administration of Nimesulide 50 to 200 mg to healthy adult volunteers. The elimination half-life of 4-Hydroxy-Nimesulide ranges from 2.89 to 4.78 hours and is generally
similar to or slightly higher than that of the parent compound (1.56 to 4.95 h).

The pharmacokinetic profile of Nimesulide is not significantly altered in children, elderly volunteers and patients with moderately impaired renal function [creatinine clearance 1.8 to 4.8 L/h (30 to 80 ml/min)]. Slight accumulation of 4-Hydroxy-Nimesulide was noted in patients with moderate renal impairment; however, the clinical significance of this finding is unknown.

**Serratiopeptidase**
Serratiopeptidase when consumed in unprotected form is destroyed by acid in the stomach. However, enteric coated granules, enable the enzyme to pass through the stomach unchanged, and be absorbed in the intestine. It is found negligibly in urine suggesting that it is transported directly from the intestine into the blood stream.

**INDICATIONS**

Nimulid - SP is indicated in conditions like:

- **Trauma Surgery**: In sports injuries, sprains, laceration, fractures, dislocation and osteoarthritis etc. It reduces inflammation and pain thus helps faster healing and repair.
- **Surgery**: Reduces Post Operative Edema at injection sites. Reduces internal tissue edema and inflammation caused at post-operative handling. Reduction in edema reduces chances of rupture at tissue site as well as risk of graft rejection along with reduction in pain.
- **Plastic Surgery**: Reduces Post Operative Edema and restores micro-circulation at the site of graft rejection.
- **Respiratory Medicine**: Breaks down complex sputum molecules in smaller peptides with lower viscosity, helping in expectorating them more easily. Reduced viscosity of secretion helps in better antibiotic penetration to enable control over stubborn infections like bronchitis, lung abscess and bronchectasis. Nimesulide helps in controlling pain and inflammation.
- **Infections**: Mucolytic activity in sinuses, ear cavities and anti-inflammatory activity in upper respiratory tract organs help in faster resolution, better antibiotic bioavailability and faster cure rates.
- **Dermatology**: Used in acute painful inflamed dermatoses.
- **Dentistry**: Helps better control over dental infections and inflammation.
- **Obstetrics & Gynecology**: The anti-inflammatory activity helps in resolution of post-partum haematomas, breast engorgements and pregnancy-related thrombophlebitis.

**CONTRAINDICATIONS**

Hypersensitivity to Nimesulide and Serratiopeptidase. Nimulid-SP is contraindicated in patients of active peptic ulcer disease, moderate to severe hepatic impairment, severe renal failure and with blood coagulation disorders.
WARNING

Usage in pregnancy and nursing mothers: No well controlled studies are available regarding the use of nimesulide or Serratiopeptidase in pregnancy and lactation. Avoid the use of Nimulid-SP in such cases.

Usage in children: Safety and efficacy of Nimesulide in children is well established. Experience with Serratiopeptidase in children is not available.

ADVERSE REACTIONS

Nimesulide: The most common adverse reactions are gastrointestinal disturbances (epigastralgia, heart burns, nausea, diarrhoea and vomiting). Dermatological reactions include rash and pruritus; central nervous system associated side effects are dizziness, somnolence and headache. Occasionally, excessive perspiration, flushing, hyperexcitability and sleep disorders have been reported. Rarely, a rise in liver enzyme levels have also been reported.

Serratiopeptidase: Hypersensitivity reactions, such as rash or redness, may infrequently occur. If such reactions occur, Nimulid-SP should be discontinued.

Gastrointestinal: Anorexia, gastric discomfort, nausea or vomiting may infrequently occur. These can be minimised if the tablets are taken after meals.

DRUG INTERACTIONS

Nimesulide: Due to the extensive plasma protein binding Nimesulide may be displaced from the binding site by concurrent administration of Fenofibrate, Salicylic acid, Valproic acid and Tolbutamide. Moreover, Nimesulide may displace Salicylic acid, Methotrexate and Furosemide from binding sites. Nimesulide reduced the diuretic effect for concomitantly administered Furosemide. Although Nimesulide does not appear to interact with Warfarin, in clinical practice, interaction with oral anticoagulants or other highly protein bound drugs cannot be ruled out. Nimesulide may cause enzymatic induction of Theophylline when administered concomitantly with it. Nimesulide had no significant effect on fasting blood and glucose tolerance in patients treated with anitdiabetic agents.

Serratiopeptidase: With anticoagulative agents, it may increase anticoagulative effect and therefore Nimulid-SP must not be used in such patients.

OVERDOSAGE AND TREATMENT

No data is available on overdosage toxicity. In the event of an overdosage the stomach may be emptied and symptomatic treatment should be given.

DOSAGE AND ADMINISTRATION

1 capsule, 2 - 3 times daily after meals. Dose to be adjusted according to age or symptoms or as directed by the physician.

STORAGE INSTRUCTIONS
Store at a temperature below 25°C, protect from light and moisture.

PRESENTATION

Available in blister strips of 10 x 10’s capsules.

REFERENCES
