

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

Nimulid-MR
Nimesulide and Tizanidine Tablets



DESCRIPTION

Nimulid - MR is a fixed dose combination (FDC) of Nimesulide and Tizanidine. Nimesulide is chemically *N*-(4-Nitro-2-phenoxyphenyl)methane sulphonamide.

Tizanidine is chemically 5-chloro-4-(2-imidazolin-2-ylamino)-2,1,3-benzothiadiazole.

Nimulid-MR is a pale yellow / yellow coloured, round, flat, bevel edged, uncoated, bilayered tablet.

COMPOSITION

Each uncoated bilayered tablet contains:

Nimesulide 100 mg
Tizanidine Hydrochloride
equivalent to Tizanidine2 mg

PHARMACOLOGY

Nimesulide

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. Nimesulide has exhibited potency similar to or greater than that of Indomethacin, Diclofenac, Piroxicam and Ibuprofen.

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

- Selective cyclooxygenase 2 inhibition.
- 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 (PD-4) inhibition.

Tizanidine

Tizanidine is a central α_2 - adrenoceptor agonist used as a myotonolytic agent in patients with spasticity associated with multiple sclerosis and cerebral or spinal damage. Muscle reflexes (particularly polysynaptic reflexes) are depressed by Tizanidine, presumably via both spinal and supraspinal effects. Investigations into the site and mode of action of Tizanidine have provided new insights into the interplay between noradrenergic and glutamatergic mechanisms as they relate to the control of muscle tone and reflex activity. Tizanidine exhibits muscle relaxant activity in both animals and humans without accompanying pronounced sedation or cardiovascular action.

RATIONALITY

Various inflammatory painful conditions in which NSAIDs are used are often accompanied with muscle spasm. Since, Tizanidine is a myotonolytic agent and is helpful in management of muscular spasm, the combination of the two drugs will be helpful in managing such conditions. Tizanidine has been found to possess antinociceptive activity in animal models as well as clinical trials. It is seen that the overall consumption of NSAIDs for the management of pain is reduced when Tizanidine is given in combination to NSAIDs. The half-life of Nimesulide (1.56 to 4.95 hr) and Tizanidine (2.12 to 4.2 hr) fall in the same range and hence, the time course of action of the two drugs might be similar. Tizanidine helps in improving the gastric safety profile of NSAIDs when given with them. The FDC provides simple drug regimen as compared to individual drugs taken together leading to better patient compliance. Hence, it can be said that Nimesulide and Tizanidine show synergistic potential which is one of the most important factors 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. 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 (\approx 70%) or the faeces (\approx 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. 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)].

Tizanidine - The dosage, plasma concentration and antispastic activity of Tizanidine are related in individual patients but not between patients. Moderate interpatient variation has been demonstrated in the pharmacokinetics of Tizanidine, but maximum plasma concentrations appear to be reached in 0.75 to 2 hours after administration. Between 53 and 66% of the dose is absorbed and food has no effect on the pharmacokinetics of this drug.

The bioavailability of Tizanidine is estimated to be 21% and there is a low propensity for plasma protein binding (about 30%). Extensive first-pass metabolism of Tizanidine occurs, with less than 3% of unchanged drug excreted. The metabolites have no pharmacological activity. Total recovery analysis indicated that 19 to 23% of the administered dose is excreted in the faeces, and 53 to 66% in the urine. The elimination half-life ranges from 2.1 to 4.2 hours in patients with normal renal function compared with a mean value of 13.6 hours in those with renal impairment (Creatinine clearance < 1.5L/h)

INDICATIONS

Nimulid-MR is indicated in conditions associated with muscle spasm such as fractures, sprains, spondylitis, lumbago (lower back and buttock pain), rheumatoid arthritis, postoperative trauma, sports injuries.

CONTRAINDICATIONS AND PRECAUTIONS

Hypersensitivity to any of the ingredients of the preparation. Nimulid-MR is contraindicated in patients of active peptic ulcer disease, moderate to severe hepatic impairment and severe renal failure. Because of significant effect on impairment of performance, patients should be cautioned about engaging in activities requiring alertness (e.g. driving a vehicle or operating a machinery). Nimulid - MR should be used with great caution in patients with compromised renal function, cirrhosis of liver, congestive heart failure, renovascular disease or those who are volume or salt depleted. It is important to monitor hepatic injury parameters when using Nimulid-MR. Therefore, it is recommended that while on Nimulid-MR therapy, the serum levels of liver function enzymes (liver function test) be assayed periodically. Discontinue the drug immediately in cases with worsening liver tests.

WARNING

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

Usage in children: Safety and efficacy of Nimesulide in children is well established. Experience with Tizanidine in children is still limited.

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.

Tizanidine - Side effects with the doses prescribed for muscle weakness, are usually mild. The most common adverse effects associated with Tizanidine are dry mouth, somnolence, drowsiness, hallucinations, muscle weakness and dizziness. Clinically significant increase in liver enzymes might occur. Intravenous and oral administration of Tizanidine in animal models has shown an initial transient hypertensive response accompanied by tachycardia in some studies followed by gradual hypotensive effect and bradycardia in most of the investigations.

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 antidiabetic agents.

Tizanidine - Coadministration of other antihypertensive drugs including diuretics may cause hypotension and bradycardia. Other sedatives such as alcohol, barbiturates and benzodiazepines may enhance the sedation or drowsiness caused by Tizanidine.

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

The usual oral dosage of Nimulid-MR in adults is 1 to 2 tablets twice daily or as directed by the physician.

STORAGE INSTRUCTIONS

Store at a temperature below 30°C, protect from light and moisture.

PRESENTATION

Blister pack of 10 X 10 tablets

REFERENCES

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