DESCRIPTION

NIMULID (Nimesulide) is described chemically as N-(4-Nitro-2-phenoxyphenyl) methanesulphonamide. It has the following structure:

![Chemical structure of Nimesulide]

Nimesulide is a yellowish crystalline powder. Nimesulide is practically insoluble in water, freely soluble in acetone and slightly soluble in ethanol. The empirical formula for Nimesulide is C_{13}H_{12}N_{2}O_{5}S, and the molecular weight is 308.31. Nimesulide suspension is yellow coloured, viscous, flavoured suspension filled in amber glass bottle. Nimesulide suspension contains following inactive ingredients: Sorbitol, Glycerin, Sucrose, Citric acid, Quinoline yellow, Mango flavour, Parabens and Xanthan gum.

Each 5 ml (Approx. one teaspoonful) contains:

Nimesulide BP ............ 50mg

In a palatable base

CLINICAL PHARMACOLOGY

*Mechanism of Action*

Nimesulide is a sulfonanilide non-steroidal anti-inflammatory drug whose anti-inflammatory analgesic and antipyretic activities have been demonstrated in several widely used animal experimental models. At the recommended dose of 5 mg/kg/day, it is as effective an antipyretic and anti-inflammatory agent as classical NSAIDs, and a well-tolerated drug with fewer side effects as evidenced by a number of controlled and non-controlled comparative trials. Nimesulide is a unique NSAID, not only due to its chemical structure but also because of its specific affinity to inhibit Cyclooxygenase-2 thus exerting milder effects on the gastrointestinal mucosa. Nimesulide appears to exert its therapeutics effects through a variety of mechanisms viz:
• Selective Cyclooxygenase-2 inhibitor
• Reduced generation of superoxide anions by stimulated polymorphonuclear leucocytes
• Inhibition of platelet aggregation factor synthesis by activated cells
• Scavenger of inactivation of α1-protease inhibitor
• Inhibition of histamine release
• Inhibition of protein kinase C through inhibition of phosphodiesterase type IV
• Reduced degradation of cartilage matrix through inhibition of metalloprotease synthesis
• Potent inhibition of induced platelet aggregation
• Prevention of bradykinin/cytokine induced hyperalgesia of nerves (inhibiting release of TNF-α)

Pharmacokinetics

Absorption

Nimesulide seems to be more rapidly and extensively absorbed in children. After oral administration of a 50mg dose, mean maximum plasma concentration (C_{max}) value of 3.45 mg /L was achieved at 1.93 hours (T_{max}). The area under the plasma concentration time curve (AUC_{0-∞}) was found to be 18.4 mg/h.L. Nimesulide is absorbed at a similar rate and to the same extent whether administered in tablet, suspension or granular form.

Metabolism

Nimesulide is almost exclusively metabolized and cleared by the liver. Metabolic biotransformation of Nimesulide in the liver can occur at both the phenoxy ring moiety and the aromatic nitro group. The major oxidative metabolite found in the plasma is para-hydroxy Nimesulide in both free and conjugated forms and this metabolite also appears to contribute to the anti-inflammatory activity of the compound.

Elimination

After oral administration of Nimesulide 50 mg, the terminal elimination half-life (t_{β}) of Nimesulide is shorter in children i.e. 2.36 hrs. Nimesulide is mainly eliminated by the renal route. Para hydroxy Nimesulide has a terminal elimination half-life of 7.91 hours (t_{β}).

Special populations

Gender

Gender does not appear to substantially affect the rate or the extent of Nimesulide absorption, distribution and elimination. It is noteworthy, however, that the mean peak plasma concentration, total plasma clearance and volume of distribution in the post-distributive phase were higher in females than in males.

Renal Insufficiency

Pharmacokinetic profiles of Nimesulide and its hydroxy metabolites are not altered significantly in patients with moderate renal failure.

Hepatic Insufficiency

Use of Nimesulide is not recommended in patients with moderate or severe hepatic insufficiency.

DRUG INTERACTION

Extensively plasma protein bound drugs

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.

Furosemide

Nimesulide reduced the diuretic effect for concomitantly administered furosemide.
Digoxin Concomitant administration of Nimesulide and Digoxin showed no effect on serum Digoxin concentrations at steady state.

Warfarin

Nimesulide does not appear to interact with Warfarin, in clinical practice; although interaction with oral anticoagulants or other highly protein bound drugs cannot be ruled out.

Theophylline

Nimesulide may cause enzymatic induction of Theophylline when administered concomitantly with it.

Antidiabetic agents

Nimesulide had no significant effect on fasting blood and glucose tolerance in patients treated with antidiabetic agents.

INDICATIONS AND USAGE

Nimesulide is indicated in reducing pain, fever and inflammatory symptoms of:

- Respiratory tract infections
- Otorhinolaryngological diseases
- Soft tissues and oral cavity inflammation
- Phlebitis / thrombosis
- Postoperative pain states
- Sports injuries.

CONTRAINDICATIONS

- History of allergy to NSAIDs
- History of nasal polyps, angiodema and/or bronchospastic reactivity to any NSAID
- Hypovolaemia/dehydration (>10% total body weight)
- Peptic ulcer disease or Renal insufficiency
- Hepatic insufficiency
- Bleeding disorders
- Concomitant administration of drugs known to interact with NSAIDs/Nimesulide such as anti-diabetics and anti-epileptics.
- History of allergy to any of its component.

WARNING

Gastrointestinal (GI) Effects- Risk of GI Ulceration, Bleeding and Perforation

Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to be taken if they occur. NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. To minimize the potential risk for an adverse GI event, the lowest effective dose should be
used for the shortest possible duration. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.
Studies have shown that patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding and who use NSAIDs, have a greater than 10-fold higher risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmaco-epidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.
The results of clinical trials suggest that Nimesulide is better tolerated than classical NSAIDs, especially in regards to gastrointestinal adverse reactions. Various studies have found that gastric mucosal damage by Nimesulide is either similar to placebo or better than reference compounds.\textsuperscript{11,12}

**Anaphylactoid Reactions**
As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to Nimesulide. In post-marketing experience, rare cases of anaphylactoid reactions and angioedema have been reported in patients receiving Nimesulide. Emergency help should be sought in cases where an anaphylactoid reaction occurs.

**Advanced Renal Disease**
No safety information is available regarding the use of Nimesulide in patients with advanced kidney disease. Therefore, treatment with Nimesulide is not recommended in these patients. If Nimesulide therapy must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS, Renal Effects).

**PRECAUTIONS**

**Hepatic Effects**
Borderline elevations of one or more liver tests may occur in up to 15\% of patients taking NSAIDs, and notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1\% of patients in clinical trials with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported with NSAIDs as well as Nimesulide.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with Nimulid. Use of Nimesulide is not recommended in patients with moderate or severe hepatic insufficiency. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), Nimesulide should be discontinued.

**Renal Effects**
Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. Caution should be used when initiating treatment with Nimesulide in patients with considerable dehydration. Caution is also recommended in patients with pre-existing kidney disease, nephritic syndrome, chronic renal failure, congestive heart failure or diuretic induced sodium depletion.

**Preexisting Asthma**
Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal.
Cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients. However, Nimesulide has demonstrated better tolerability when administered to patients with this form of aspirin sensitivity.\textsuperscript{13,14}

**Information for Patients**

Patients should promptly report signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, unexplained weight gain, or edema to their physicians.

Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

Patients should also be instructed to seek immediate emergency help in the case of an anaphylactoid reaction (see WARNINGS).

**Laboratory Tests**

Because serious hepatic toxicity can occur without warning symptoms, physicians should monitor for signs or symptoms of hepatic toxicity.

**CAUTION**: Coadministration with other potentially hepatotoxic drugs should be avoided.

**ADVERSE REACTIONS**

Between the years 1985 and 2000, a total number of 192 hepatic ADRs were reported with Nimesulide. Out of these 81 were considered to be serious and 111 as non-serious. Based on the mean treatment time of 2 weeks for acute treatment and 6 months for chronic treatment, the incidence of adverse effect was found to be 0.1 per 100,000 cases. For most other NSAIDs, the absolute risk is 1-4 per 100,000 cases.\textsuperscript{15}

The adverse effect profile of Nimesulide in Indian population in children was similar to that reported for all age groups. The adverse effects reported in 4097 case report forms were gastrointestinal (3.1%), vomiting (1.34%), burning stomach / irritation in stomach (0.60%), abdominal pain (0.50%), diarrhoea (0.40%), nausea (0.17%), black stools (0.10%), hematemesis (0.02%), skin and mucous membrane (1.7%), itching / rash / urticaria (1.50%), cold and clammy skin (0.10%), stomatitis (0.04%), yellow discolouration (0.04%), dry red lips (0.02%), bleeding gums (0.02%), renal (0.3%), generalised edema (0.10%), hematuria (0.10%), reduced urine output (0.04%), burning micturition (0.04%), nephritis (0.02%), CNS (0.4%), drowsiness (0.12%), dizziness (0.10%), irritability (0.15%), heavy headedness (0.02%), others (1.3%), puffiness of face / eyelids (0.70%), hypothermia (0.31%), excessive sweating (0.17%), muscle pain (0.07%), chest pain (0.02%), joint swelling (0.02%), peripheral cyanosis (0.02%) and worsening (0.02%).

Out of these only patients with hypothermia, hemetemesis and muscle pains required hospitalization, but all subsided after stopping the drug.\textsuperscript{16}

**OVERDOSAGE AND TREATMENT**

No data is available on overdosage toxicity. In the event of overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required.

**dosage AND ADMINISTRATION**

The usual oral dosage of Nimesulide in adults is 5 mg/Kg body weight in 2 or 3 daily divided doses.

**STORAGE INSTRUCTIONS**

Store in a cool and dark place.
REFERENCES