DESCRIPTION

Nimesulide is described chemically as N- (4-nitro-2-phenoxyphenyl) methane sulfonamide.

Nimesulide is a yellowish crystalline powder. It is practically insoluble in water, freely soluble in acetone and slightly soluble in ethanol. The empirical formula for Nimesulide is C13H12N2O5 S, and the molecular weight is 308.311.

Willgo is light yellow/ reddish brown colored, round, biconvex, uncoated bilayered tablet.

COMPOSITION

Each uncoated extended release* tablet contains:

Nimesulide BP............................ 200 mg

Colour : Iron Oxide Red

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 200 mg per day, it is as effective as an analgesic and anti-inflammatory agent as classical NSAIDs, and a well-tolerated drug with fewer side effects as evidenced by a number of controlled and un-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 is the only NSAID able to affect all the mediators of pain and inflammation. Nimesulide inhibits COX-1 to some extent, leading to better treatment of inflammatory pain. Nimesulide also reduces pain at central level through a spinal supraspinal mechanism. Moreover, Nimesulide also has a potent and long lasting anti-pyretic affect.
Nimesulide appears to exert its therapeutic effects through a variety of mechanisms viz⁴:

- Preferential Cyclooxygenase-2 inhibition at its origin (gene Expression)
- Reduced generation of superoxide anions by stimulated polymorphonuclear leucocytes
- Inhibition of platelet aggregation factor synthesis by activated cells
- Nimesulide induces production of nitric oxide.
- Scavenger of inactivation of alpha 1-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-alpha).

The drug reduces superoxide anion generation by activated neutrophils without influencing their phagocytic or chemotactic responsiveness and inhibits the leucocyte respiratory burst through inhibition of phosphodiesterase (PDE) type IV, the principal enzyme responsible for the degradation of leucocyte cAMP.

Also, Nimesulide protects chondrocytes, the cells that in normal conditions produces cartilage.

**PHARMACOKINETICS**

**Absorption**

Nimesulide extended release* tablet 200 mg when taken 10 minutes after food, started exhibiting appreciable concentrations within 1 hour and reached a mean peak concentration ($C_{\text{max}}$) of 8.87 µg/ml at 5.33 hours ($t_{\text{max}}$). The concentration of Nimesulide in the plasma at 12 hrs and 24 hrs for the extended release* tablet was 4.02 µg/ml and 0.74 mcg/ml, respectively. The concentration of para hydroxy Nimesulide in the plasma at 12 hrs and 24 hrs for the extended release* tablet was 7.95 µg/ml and 3.54 µg/ml, as against 7.47 and 2.38 for the conventional release formulation, respectively. The AUC values for Nimesulide extended release* tablet 200 mg formulation at 0 - 24 hours was 92.1 µg/ml.hr as against 76.7 µg/ml.hr for the conventional release formulation.⁵

After oral administration of a 200mg dose in tablet form, urinary recovery was approximately 80% and faecal recovery about 20% over a 3-day period. Thus by mass balance, it can be deduced that at least 80% of the administered dose was absorbed by the gastrointestinal tract. Given that Nimesulide and/or its metabolites may also be excreted in the bile, the extent of Nimesulide absorption after oral administration is likely to be greater than 80%.

**Effect of Food**

When Nimesulide extended release* 200mg was taken after meals, it showed appreciable and effective blood levels for Nimesulide above 1 µg/ml, which was achieved within 1 hour indicating an early onset of action. The levels above 1 mcg/ml were maintained for a duration which extended over 18 - 20 hours and more, as expected.

In view of above, Nimesulide extended release* 200mg when administered after meals at bed time, is expected to provide immediate relief of pain as well as relief in the morning with ease, as peak plateau levels will be achieved and maintained nearing the morning hours, when the
pain and stiffness is at its zenith.

**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**

The elimination half life for Nimesulide extended release tablet was 5.2 hours as against 3.97 hours for the conventional release formulation, as anticipated at the time this formulation was developed. Moreover, the extended release formulation showed a mean residence time of 10.39 hours as against 7.95 hours for the conventional release formulation. This clearly suggests that due to the longer residence time of the extended release formulation in the body, sustained blood levels for Nimesulide are expected to be maintained for a much longer duration of time.

**PHARMACOKINETICS IN SPECIAL POPULATIONS**

**Geriatric**

The pharmacokinetic profile of Nimesulide and its para-hydroxy metabolite was similar in the elderly and young healthy volunteers and suggest that no Nimesulide dosage adjustment is necessary in patients less than 80 years of age.

**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.

**Patients with renal insufficiency**

The pharmacokinetic profile of Nimesulide in volunteers with moderate renal impairment was assessed in two non-blind studies. In the first study, a single dose of 100mg of Nimesulide was administered to 10 patients between 18 to 65 years of age. The apparent total clearance (Cl\text{tot}) for Nimesulide was significantly lower (2.9 vs 4.8L/h) and the terminal elimination half-life for hydroxy Nimesulide was significantly longer (6.05 vs 4.02h) in renally impaired patients.

The second investigation assessed the pharmacokinetic profile of repeat doses of Nimesulide in 10 patients between 49 to 69 years of age. Analysis of data showed that the AUC\text{0-∞} for hydroxy Nimesulide was slightly greater (19.7 vs15.4mg/L.h) following repeat dose administration. The urinary clearance for hydroxy Nimesulide at steady state was higher than that after the first dose (1.02L/h).

Results of these studies suggested that the pharmacokinetic profiles of Nimesulide and its hydroxy metabolites are not altered significantly in patients with moderate renal failure.

**DRUG INTERACTIONS**

**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 reduces the diuretic effect of 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:

- Chronic arthritis (Osteoarthritis)
- Rheumatoid arthritis

**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
- Renal insufficiency
- Hepatic insufficiency
- Bleeding disorders
- Concomitant administration of drugs known to interact with NSAIDs/Nimesulide such as anti-diabetics and anti-epileptics.

**WARNINGS**

**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 non-steroidal 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 with regard to gastrointestinal adverse reactions. Various studies have demonstrated that gastric mucosal damage by Nimesulide is either similar to placebo or better than reference compounds.\textsuperscript{10,11}

**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).

**Pregnancy**

In late pregnancy, Nimesulide should be avoided because it may cause neonatal as well as perinatal toxicity. Nimesulide use in pregnant women should only be done if the potential benefits outweigh the risks and under medical supervision.

**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 Nimesulide. 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 non-steroidal 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.

Pre-existing 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 non-steroidal 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.\(^{12,13}\)

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.

ADVERSE REACTIONS

World wide, the majority of adverse reactions recorded affected the digestive system followed by the skin and the nervous system. Of the 17 ADR reports ascribed to Nimesulide as received
by the national pharmacovigilance center of the WHO, 5 were of the skin and 4 of the liver. Others were peripheral edema (2), stomatitis (2), paresthesia (1), thrombocytopaenic purpura (1), irritability (1) and headache / reduced visual activity (1). No adverse GI reactions have been reported. Of the hepatic ADR’s reported; two cases were compatible with Reye’s syndrome. Nimesulide may also cause acute hepatitis and an elevation in liver enzymes 14.

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 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 discoloration (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, hematemesis and muscle pains required hospitalization, but all subsided after stopping the drug 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 oral recommended dose of Willgo (Nimesulide extended release* tablets) in adults is one tablet daily after meals at bed time.

The tablet should be swallowed whole and not to be chewed.

STORAGE INSTRUCTIONS

Store at a temperature below 30°C, protect from light and moisture. Keep the medicine out of reach of children.
REFERENCES

5. Gupta SK. A comparative pharmacokinetic evaluation of Nimesulide extended release* 200 mg (Willgo) tablets vs Nimesulide conventional release 200 mg (Nimulid DS 200 mg) tablets (Manufactured by Panacea Biotec Ltd., India) in healthy human volunteers. Data on file.