NISE®
(Nimesulide)
نائیس

COMPOSITION

Nise 100 mg Tablet
Each film coated tablet contains: Nimesulide BP……100 mg
(PharmEvo Specs.)

Warning : Recommended oral dose of Nimesulide is 100mg twice daily for 15 days. If the prescriber warrants a longer use of the drug, liver function test must be performed periodically thereafter to assess the impact of the drug on the liver. Nimesulide is contraindicated in patients suffering from liver problems.

DESCRIPTION
NISE tablets contain Nimesulide, a relatively COX-2 selective, nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. It is chemically designated as N-(4-Nitro-2-phenoxyphenyl)methane sulfonamide . The molecular formula is $C_{13}H_{12}N_2O_5S$.

CLINICAL PHARMACOLOGY

Mechanism of Action
Nimesulide is characterized by a unique multifactorial mode of action which targets a number of key mediators of the inflammatory process. Nimesulide is able to inhibit cyclo-oxygenase, the enzyme responsible for the synthesis of prostaglandin. Both in vitro and in-vivo, nimesulide showed to inhibit preferentially the COX-2 enzyme, which is expressed during inflammation, with a minimal activity against COX-1, which plays a protective role in the gastric mucosa.
Nimesulide has demonstrated many other pharmacological effects that are the basis for its clinical activities.
• Inhibition of phosphodiesterase (PDE) type IV,
• Reduced generation of superoxide anion (O2•),
• Scavenging of hypochlorous acid,
• Inhibition of proteases (elastase, proteinase),
• Inhibition of histamine release from human basophil and mast cells,
• Inhibition of histamine activity,
• Activation of glucorticoid receptor (GR) system,
• Inhibition of the synthesis and relelase of the Substance P (SP).

Inflammation is a complex and multimediated process and as nimesulide shows a multifactorial mode of action the intensity of this can be reduced in a particularly effective way.
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 able to affect all the mediators of pain and inflammation and has a desired and long lasting analgesic and anti-pyretic effect. Nimesulide inhibits COX-1 to some extent; leading to better treatment of inflammatory pain. Nimesulide also reduces pain at central level through a spinal and supraspinal mechanism.

Pharmacokinetics

Absorption
Nimesulide is well absorbed when given by mouth. After a single dose of 100mg nimesulide a peak plasma level of 3-4 mg/l is reached in adults after 2-3 hours. AUC = 20 - 35 mg h/l.

Distribution
Nimesulide is up to 97.5% bound to plasma proteins.

Metabolism
Nimesulide is extensively metabolized in the liver following multiple pathways, including cytochrome P450 (CYP) 2C9 isoenzymes. Therefore, there is the potential for a drug interaction with concomitant administration of drugs which are metabolized by CYP2C9. The main metabolite is the para-hydroxy derivative which is also pharmacologically active. The lag time before the appearance of this metabolite in the circulation is short (about 0.8 hour) but its formation constant is not high and is considerably lower than the absorption constant of nimesulide. Hydroxynimesulide is the only metabolite found in plasma and it is almost completely conjugated and t½ is between 3.2 and 6 hours.

Elimination
Nimesulide is excreted mainly in the urine (approximately 50% of the administered dose). Only 1-3% is excreted as the unmodified compound. Hydroxynimesulide, the main metabolite is found only as a glucuronate. Approximately 29% of the dose is excreted after metabolism in the faeces.

INDICATIONS

NISE (Nimesulide) is indicated in the treatment of:

• Treatment of acute pain, including painful conditions associated with inflammation such as post-operative dental pain, post-surgical pain, post-traumatic conditions (acute joint and soft tissue injuries), painful extra-articular disorders, acute bursitis, tendinitis etc.

• Primary dysmenorrhoea.

DOSAGE AND ADMINISTRATION

Adults
Usual oral dose of Nimesulide is 100mg twice daily, for no more than 15 days.

Dosage adjustment and dosing consideration in special populations

Children (< 12 years)
Nimesulide is contraindicated in children below 12 years and in patients suffering from liver problems.

Adolescents (from 12 to 18 years)
On the basis of the kinetic profile in adults and on the pharmacodynamics characteristics of nimesulide, no dosage adjustment in these patients is necessary.

Elderly
No dosage adjustment is required in the elderly

Renal impairment
On the basis of pharmacokinetics, no dosage adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance of 30-80 ml/min), while Nimesulide is contraindicated in case of severe renal impairment (creatinine clearance < 30ml/min)

Hepatic impairment
The use of Nimesulide is contraindicated in patients with hepatic impairment

CONTRAINDICATIONS
• Hypersensitivity to nimesulide.
• History of hypersensitivity reactions (e.g. bronchospasm, rhinitis, urticarial, nasal polyps) in response to acetylsalicylic acid or other non-steroidal anti-inflammatory drugs
• History of hepatotoxic reactions to nimesulide
• Concomitant exposure to other potentially hepatotoxic substances,
• Alcoholism, drug addiction
• Cerebrovascular bleeding or other active bleeding or bleeding disorders
• Severe coagulation disorders
• Severe heart failure
• Severe renal impairment
• Hepatic impairment
• Patients with fever and/or flu-like symptoms
• Children under 12 years
• The third trimester of pregnancy and breast feeding
• Active gastric or duodenal ulcer, a history of recurrent ulceration or gastrointestinal bleeding

WARNINGS AND PRECAUTIONS

• Rarely Nimesulide has been reported to be associated with serious hepatic reactions, including very rare fatal cases. Patients who experience symptoms compatible with hepatic injury during treatment with Nimesulide (e.g. anorexia, nausea, vomiting, abdominal pain, fatigue, dark urine) or patients who develop abnormal liver function tests should have treatment discontinued. These patients should not be rechallenged with nimesulide. Liver damage, in most cases reversible, has been reported following short exposure to the drug.

• Concomitant administration with known hepatotoxic drugs, and alcohol abuse must be avoided during treatment with Nimesulide treatment, since either may increase the risk of hepatic reactions.

• During therapy with Nimesulide, patients should be advised to refrain from other analgesics. Simultaneous use of different NSAIDs is not recommended.

• Gastrointestinal bleeding or ulceration / perforation can occur at any time during treatment with or without warning symptoms or a previous history of gastrointestinal events. If gastrointestinal bleeding or ulceration occurs, nimesulide should be discontinued. Nimesulide should be used with caution in patients with gastrointestinal disorders, including history of peptic ulceration, history of gastrointestinal haemorrhage, ulcerative colitis or Crohn's disease.

• In patients with renal orcardiac impairment, caution is required since the use of Nimesulide-may result in deterioration of renal function. In the event of deterioration, the treatment should be discontinued.

• Elderly patients are particularly susceptible to the adverse effects of NSAIDs, including gastrointestinal haemorrhage and perforation, impaired renal, cardiac and hepatic function. Therefore, appropriate clinical monitoring is advisable.

• As nimesulide can interfere with platelet function, it should be used with caution in patients with bleeding diathesis. However, Nimesulide is not a substitute for acetylsalicylic acid for cardiovas-

cular prophylaxis.

• Patients receiving Nimesulide who develop fever and/or flu like symptoms should discontinue treatment.

• The use of Nimesulide may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Nimesulide should be considered

• No studies on the effect of Nimesulide on the ability to drive or use machines have been performed. However, patients who experience dizziness, vertigo or somnolence after receiving Nimesulide should refrain from driving or operating machines.

ADVERSE REACTIONS

Blood disorders
Rare: anemia*, eosinophilia*
Very rare: Thrombocytopenia, Pancytopenia, Purpura
Immune system disorders
Rare: Hypersensitivity*
Very rare: Anaphylaxis
Metabolism and nutrition disorders
Rare: Hyperkalemia*
Psychiatric disorders
Rare: Anxiety*, Nervousness*, Nightmare*
Nervous system disorders
Uncommon: Dizziness*
Very Rare: Headache, Somnolence, Encephalopathy (Reye's syndrome)
Eye disorders
Rare: Vision blurred*
Very rare: Visual disturbance
Ear and labyrinth disorders
Very rare: Vertigo
Cardiac disorders
Rare: Tachycardia*
Vascular disorders
Uncommon: Hypertension*
Rare: Haemorrhage*, Blood pressure fluctuation*, Hot flushes*
Respiratory disorders
Uncommon: Dyspnoea *
Very rare: Asthma, Bronchospasm
Gastrointestinal disorders
Common: Diarrhoea*, Nausea*, Vomiting*
Uncommon: Constipation*, Flatulence*, Gastritis*, Gastrointestinal bleeding, Duodenal ulcer and perforation, Gastric ulcer and perforation
Very rare: Abdominal pain, Dyspepsia, Stomatitis, Melaena
Hepatobiliary disorders
Common: Hepatic enzymes increased
Very rare: Hepatitis, Fulminant hepatitis (including fatal cases) Jaundice, Cholestasis
Skin and subcutaneous tissue disorders
Uncommon: Pruritus*, Rash*, Sweating increased*
Rare: Erythema*, Dermatitis*
Very rare: Urticaria, Angioneurotic oedema , Face oedema, Erythema multiforme , Stevens Johnson syndrome, Toxic epidermal necrolysis
Renal and urinary disorders
Rare: Dysuria*, Haematuria*, Urinary retention*
Very rare: Renal failure, Oliguria, Interstitial nephritis
General disorders
Uncommon: Oedema*
Rare: Malaise*, Asthenia*
Very rare: Hypothermia
Investigations
Common: Hepatic enzymes increased*

**Frequency based on clinical trials*

DRUG INTERACTIONS

Pharmacodynamics interactions
Patients receiving warfarin or similar anticoagulant agents or acetylsalicylic acid have an increased risk of bleeding complications, when treated with Nimesulide. Therefore this combination is not recommended and is contraindicated in patients with severe coagulation disorders. If the combination cannot be avoided, anticoagulant activity should be monitored closely.

Pharmacodynamics/pharmacokinetic interactions with diuretics
In healthy subjects, nimesulide transiently decreases the effect of furosemide on sodium excretion and to a lesser extent, on potassium excretion and reduces the diuretic response. Co-administration of nimesulide and furosemide results in a decrease (of about 20%) of the AUC and cumulative excretion of furosemide, without affecting its renal clearance. The concomitant use of furosemide and Nimesulide requires caution in susceptible renal or cardiac patients.

Pharmacokinetic interactions with other drugs:
• Non-steroidal anti-inflammatory drugs have been reported to reduce the clearance of lithium, resulting in elevated plasma levels and lithium toxicity. If Nimesulide are prescribed for a patient receiving lithium therapy, lithium levels should be monitored closely.
• Nimesulide inhibits CYP2C9, the plasma concentrations of drugs that are substrates of this enzyme may be increased when Nimesulide are used concomitantly.
• Caution is required if nimesulide is used less than 24 hours before or after treatment with methotrexate because the serum level of methotrexate might increase and therefore, the toxicity of this drug might increase.
• Due to their effect on renal prostaglandins, prostaglandin synthetase inhibitors like nimesulide may increase the nephrotoxicity of cyclosporines.

USE IN SPECIAL POPULATIONS

Pregnancy
The use of Nimesulide is contraindicated in the third trimester of pregnancy. Like other NSAIDs Nimesulide is not recommended in women attempting to conceive. As with other NSAIDs, known to inhibit prostaglandin synthesis, nimesulide may cause premature closure of the ductus arteriosus, pulmonary hypertension, oliguria, oligoamnios, and increased risk of bleeding, uterine inertia and peripheral oedema. There have been isolated reports of renal failure in neonates born to women taking nimesulide in late pregnancy. Therefore, the potential risk for humans is unknown and prescribing the drug during the first two trimesters of pregnancy is also not recommended.

Nursing mothers
It is not known whether nimesulide is excreted in human milk. Nimesulide is contraindicated during breastfeeding.

OVER DOSAGE
Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactic reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose. Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. No information is available regarding the removal of nimesulide by hemodialysis, but based on its high degree of plasma protein binding (up to 97.5%) dialysis is unlikely to be useful in overdose. Emesis and/or activated charcoal (60 to 100 g in adults) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinization of urine, hemodialysis, or haemoperfusion may not be useful due to high protein binding. Renal and hepatic function should be monitored.

PRESENTATION
Nise 100 mg Tablet: Pack of 20 tablets.

INSTRUCTIONS:
Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from heat, light and moisture.
Store below 30°C.

For more information on our products
call PharmAssist helpline 0800-82222
Monday to Friday 9:00 am to 6:00 pm
or email us at : pharmassist@pharmevo.biz

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Our dream, a healthier society

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