NIMESULIDE

INDICATIONS:

- **Acute Pain**

  Nimesulide is used to relieve pain and swelling of joints and muscle in adults.

- **Osteoarthritic Pain**

  Nimesulide is used to relieve the symptomatic pain associated with Osteoarthritis in adults.

- **Primary Dysmenorrhea**

  Nimesulide is used to relieve acute pain associated with menstruation.

SAFETY ALERT:

1. **Adverse Drug Reactions**:
2. **Drug interactions**:

- *Pharmacodynamic interactions*
- *Other non steroidal anti-inflammatory drugs (NSAIDs) :*
- **The combined use of** Mesulid (see section 4.4) with other non steroidal anti-inflammatory drugs, including acetylsalicylic acid given at anti-inflammatory doses (≥ 1g as single intake or ≥ 3g as total daily amount) is not recommended.
- *Corticosteroids*
- Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).
- *Anti-coagulants:*
- NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4). Patients receiving warfarin or similar anticoagulant agents or acetylsalicylic acid have an increased risk of bleeding complications, when treated with Mesulid. Therefore this combination is not recommended (see also section 4.4) and is contraindicated in patients with severe coagulation disorders (see also section 4.3). If the combination cannot be avoided, anticoagulant activity should be monitored closely.
- *Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs)*: increased risk of gastrointestinal bleeding (see section 4.4).
- *Diuretics, Angiotensin Conversion Enzyme Inhibitors (ACE inhibitors) and Angiotensin II Antagonists (AIIA):*
- NSAIDs may reduce the efficacy of diuretics and that of other antihypertensive drugs. In some patients with reduced renal function (e.g. dehydrated patients or elderly subjects with impairment of renal function), concomitant administration of an ACE inhibitor and cyclo-oxygenase inhibitors may result in progression of the deterioration of renal

function, including the possibility of acute renal insufficiency, which is normally reversible. Page 4 of 8

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- The occurrence of these interactions should be taken into consideration in patients who have to take Mesulid in association with ACE inhibitors or AIIA. Consequently, this drug association should be administered with precaution, especially in elderly patients. Patients should be properly hydrated, and the need for monitoring of renal function after starting the concomitant treatment and periodically after that should be analysed.
- Pharmacokinetic interactions: effect of nimesulide on the pharmacokinetics of other drugs.
- *Furosemide:*
- 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 Mesulid requires caution in susceptible renal or cardiac patients, as described under section 4.4.
- *Lithium:*
- Non-steroidal anti-inflammatory drugs have been reported to reduce the clearance of lithium, resulting in elevated plasma levels and lithium toxicity. If Mesulid is prescribed for a patient receiving lithium therapy, lithium levels should be monitored closely.
- Potential pharmacokinetic interactions with glibenclamide, theophylline, warfarin, digoxin, cimetidine and an antacid preparation (i.e. a combination of aluminium and magnesium hydroxide) were also studied in vivo. No clinically significant interactions were observed.
- Nimesulide inhibits CYP2C9. The plasma concentrations of drugs that are substrates of this enzyme may be increased when Mesulid is 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.
- Pharmacokinetic Interactions: Effects of other drugs on the pharmacokinetics of nimesulide:
- In vitro studies have shown displacement of nimesulide from binding sites by tolbutamide, salicylic acid and valproic acid. However, despite a possible effect on plasma levels, these interactions have not demonstrated clinical significance.

3. Contraindications:

- Hypersensitivity to nimesulide or to any of the excipients.
- □ History of hypersensitivity reactions (e.g. bronchospasm, rhinitis, urticaria, 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.

- □ History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- □ Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- □ cerebrovascular bleeding or other active bleeding or bleeding disorders.

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- □ 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 breastfeeding

4. Precautions:

- The use of Mesulid with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided. In addition, patients should be advised to refrain from other concomitant analgesics.
- Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms (see section 4.2).
- Treatment should be discontinued if no benefit is seen.
- *Hepatic effects*
- Rarely Mesulid has been reported to be associated with serious hepatic reactions, including very rare fatal cases (see also section 4.8). Patients who experience symptoms compatible with hepatic injury during treatment with Mesulid (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.
- Patients receiving nimesulide who develop fever and / or flu-like symptoms should discontinue treatment.
- *Gastrointestinal effects*
- Gastrointestinal bleeding, ulceration and perforation: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of GI events.
- The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and 4.5). Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding), particularly in the initial stages of treatment.
- 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.

- Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or antiplatelet agents such as aspirin (see section 4.5).
- When GI bleeding or ulceration occurs in patients receiving Mesulid the treatment should be withdrawn.
- NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (see section 4.8 – undesirable effects).
- *Elderly:* The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2). Therefore, appropriate clinical monitoring is advisable.
- ***Cardiovascular and cerebrovascular effects***

5. Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy. Page 3 of 8

- Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example, myocardial infarction or stroke). There are insufficient data to exclude such a risk for Mesulid.
- Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with Mesulid after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).
- As nimesulide can interfere with platelet function, it should be used with caution in patients with bleeding diathesis (see also section 4.3). However, Mesulid is not a substitute for acetylsalicylic acid for cardiovascular prophylaxis.
- ***Renal effects***
- In patients with renal or cardiac impairment, caution is required since the use of Mesulid may result in deterioration of renal function. In the event of deterioration, the treatment should be discontinued (see also section 4.5).
- ***Skin Reactions***
- Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Mesulid should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.
- ***Fertility effects***
- The use of Mesulid 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 Mesulid should be considered (see section 4.6).
- Mesulid contain lactose, therefore patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.