MESULID® 100
REVISED PRODUCT INFORMATION

COMPOSITION
Each caplet of MESULID 100 contains: Nimesulide 100 mg.

Inactive Ingredients
Lactose, microcrystalline cellulose, sodium starch glycolate, hydrogenated vegetable oil, dioctyl sodium sulphosuccinate, magnesium stearate, hydroxypropyl cellulose.

ACTION
Nimesulide is a novel nonsteroidal anti-inflammatory drug (NSAID) with anti-inflammatory, anti-pyretic, and analgesic properties. Nimesulide differs from other NSAIDs by having a sulfonanilide as its functional acidic group, which endows it with a unique pharmacological profile. Nimesulide inhibits prostaglandin synthetase, also known as cyclooxygenase, which in turn limits prostaglandin production. Its cyclooxygenase inhibiting potency is considered to be intermediate when compared with other NSAIDs. However, it has recently been demonstrated that cyclooxygenase exists as two isoforms in the body, namely as COX-1 and COX-2. COX-1 is a constitutive enzyme that produces prostaglandins which are essential for the maintenance of vascular homeostasis, and normal gastric and kidney function. COX-2 is an inducible enzyme that is responsible for the release of prostaglandins during inflammation. Thus, it appears that the positive anti-inflammatory activity of NSAIDs can be attributed to their ability to inhibit COX-2 while their associated side-effects are due to their ability to inhibit COX-1. Studies have shown that nimesulide is relatively selective for COX-2 (as determined by the IC50 of COX-2 divided by the IC50 of COX-1). An important consequence of this is that prostaglandins which protect the gastric mucosa are spared, thereby resulting in the potential for less gastric injury and intolerance.

In addition, nimesulide acts as a free radical scavenger and interferes with the production of oxygen radicals by leukocytes without inhibiting leukocyte chemotaxis and phagocytosis. Since the products of free radicals directly and indirectly damage the host tissue and contribute to the maintenance of the inflammatory process, nimesulide helps protect against the tissue damage that occurs during inflammation and short-circuits the inflammatory process. In this manner, nimesulide exerts a potent anti-inflammatory effect in vivo even greater than that of its anti-prostaglandin effect.

Nimesulide is well absorbed from the gastrointestinal tract following oral administration, and peak plasma levels are obtained within 1-3 hours. The drug is extensively bound (99%) to plasma protein and has an elimination half-life of 2-5 hours. With twice-daily administration of 100mg, steady-state is achieved within 24-36 hours. Nimesulide is mainly eliminated by hepatic biotransformation, with the principal metabolite being 4-hydroxy-nimesulide. Excretion of nimesulide
metabolites in the urine and feces account for about 80% and 20% of the administered dose, respectively.

Nimesulide rapidly and effectively provides relief of pain and the signs and symptoms of inflammation associated with a wide array of disorders. Nimesulide has especially proved useful in patients who do not respond adequately to other NSAIDs, and in patients who are NSAID-intolerant due to hypersensitivity (e.g., asthmatics) or gastric intolerance.

INDICATIONS
Nimesulide is indicated for short-term use in the following indications: symptomatic osteoarthritis; painful extra-articular disorders; post-operative dental pain and inflammation; primary dysmenorrhea.

CONTRAINDICATIONS
In cases of known hypersensitivity to the active or inactive ingredients.
In children under the age of 14.
In patients with hepatic impairment or known liver disease.
In patients with severe renal impairment.
In patients with gastrointestinal bleeding, active gastric or duodenal ulcers, or a history of recurrent ulceration.
In patients with coagulation disorders (e.g., hemophilia).
Nimesulide should not be used concurrently with any known hepatotoxic drug, including other NSAIDs and alcohol.
Nimesulide should not be used concurrently or within 8 weeks of administration of amoxycillin/clavulanic acid (e.g., Augmentin).

WARNINGS
Post-marketing surveillance (PMS) reports of hepatic adverse effects have been received, following both short and long periods of therapy with nimesulide. The single best way to prevent the development of serious hepatic injury is through patient education. Physicians should caution their patients to be aware of the potential for NSAIDs to cause hepatic injury and to be alert for the development of symptoms that are indicative of such injury, including malaise, fatigue, anorexia, nausea, vomiting, “flu-like” symptoms, abdominal pain, dark urine or pale stools, pruritus, and yellowing of the skin and mucous membranes. Patients should discontinue their medicine and seek medical advice promptly should any of these symptoms occur, or if any other side effect persists more than several days. Where relevant (see Precautions), patients should be informed of the need to undergo laboratory tests every 3 weeks during therapy with Mesulid. During therapy with Mesulid, patients should be advised to refrain from using other NSAIDs, including OTC NSAIDs and “leftover” medication from previous NSAID trials, aspirin and high-dose paracetamol, and those herbal/nutraceutical preparations which may be potentially hepatotoxic.

Use in Pregnancy
Safety for use during pregnancy has not been established.
Use in Breastfeeding
It is not known whether nimesulide is excreted in breast milk. Its use during lactation is not recommended.

Use in Children
Mesulid is contraindicated in children under the age of 14 (see Contraindications).

Use in Elderly
Studies in the elderly have not indicated a need to alter the usual dose. However, because the elderly may be more susceptible to adverse effects, a reduced dosage may be appropriate in isolated cases. Elderly patients should always be supervised closely for the appearance of symptoms and changes in laboratory values suggestive of renal or hepatic impairment.

ADVERSE REACTIONS
Nimesulide is generally well tolerated. The most common adverse effects are epigastric discomfort, heartburn or abdominal cramps, nausea, vomiting and diarrhea. These effects are usually mild, transient, and rarely require treatment withdrawal.

Occasionally, skin rash, pruritus, edema, headache, dizziness, drowsiness and increases in liver enzymes have been reported. Hypersensitivity reactions, including bronchospasm, rhinitis, angioedema and urticaria have been reported rarely. Gastrointestinal hemorrhage/perforation has been reported rarely. Hepatitis has also been reported rarely, some with a fatal outcome. There have been isolated reports of bullous/erosive stomatitis, purpura, thrombocytopenia, toxic epidermal necrolysis, Stevens Johnson syndrome, hematuria, oliguria, and renal failure.

PRECAUTIONS
Nimesulide should be used with caution in patients with a history of gastrointestinal tract disease. Although rare, the possibility of gastric bleeding and/or ulceration/perforation should be kept in mind. Because nimesulide is metabolized in the liver and eliminated to a large extent (80%) by urinary excretion, patients with creatinine clearance <30 ml/min should be administered nimesulide at a reduced dosage and with special caution.

Mesulid should not be administered to patients with abnormal liver function. If the physician has any concerns that liver/renal function is abnormal, liver/renal function tests should be performed before initiating therapy with Mesulid. Where therapy with Mesulid exceeds 14 days, liver function and serum creatinine should be measured every 3 weeks. Patients whose renal function deteriorates or whose liver enzyme levels increase above the upper limit of normal should discontinue Mesulid immediately. Similarly, patients with clinical signs/symptoms consistent with hepatic injury, or systemic manifestations of hypersensitivity (eg, eosinophilia, rash, fever) should discontinue Mesulid immediately. In patients who have previously experienced hepatic impairment with Mesulid, re-challenge should never be attempted.
Like other NSAIDs, nimesulide should be used with caution in patients with congestive heart failure, hypertension, renal impairment or extracellular volume depletion, who are highly susceptible to a reduction in renal blood flow. Likewise, nimesulide should be used cautiously in patients on anticoagulant therapy (see Drug Interactions).

Most patients with known hypersensitivity to acetylsalicylic acid or other NSAIDs can safely use nimesulide. However, caution should always be exercised in such individuals. Similarly, most patients with asthma tolerate nimesulide well; however, the possibility of precipitating bronchospasm cannot be entirely excluded. In these patients the first dose should be taken under medical supervision.

**Drug Interactions**

**Nimesulide/Hepatotoxic Drugs (including Augmentin, Other NSAIDs)/Alcohol**
Nimesulide should not be used concurrently with known hepatotoxins (such as anti-convulsants (eg, valproic acid), anti-fungals (eg, ketoconazole), anti-tuberculous drugs (eg, isoniazid), tacrine, pemoline, amiodarone, methotrexate, methyldopa, etc) or with alcohol. Since all NSAIDs are potentially hepatotoxic, nimesulide should not be used concurrently with other NSAIDs. Nimesulide should not be used concurrently or within 8 weeks of administration of amoxycillin/clavulanic acid (eg, Augmentin) (see Contraindications). OTC preparations containing NSAIDs or aspirin/paracetamol (high dose) and certain herbal/nutraceutical preparations may also be potentially hepatotoxic and should likewise be avoided during nimesulide therapy.

**Nimesulide/Highly Bound Drugs**
Nimesulide is extensively bound to plasma proteins and may be displaced from binding sites by concurrently administered drugs such as fenofibrate, salicylic acid, and tolbutamide. In addition, nimesulide may displace salicylic acid from plasma proteins. However, there has been no evidence to date that such interactions have clinical significance. There is no evidence that nimesulide affects fasting blood sugar and glucose tolerance in diabetic patients treated with various sulfonylureas.

**Nimesulide/Furosemide**
Nimesulide may decrease the oral bioavailability of furosemide and the natriuretic and diuretic response to furosemide.

**Nimesulide/Warfarin**
Nimesulide does not usually affect the response to warfarin; however since a few patients may show an increase in anti-coagulant effect, it is recommended that the patient's coagulation status be monitored when the two drugs are given together.

**Nimesulide/Aspirin/Other NSAIDs**
Concurrent use of two or more NSAIDs, including aspirin, may increase the risk of gastrointestinal, hepatic and other adverse effects.

**Nimesulide/Phenytoin**
Nimesulide, like other NSAIDs, can potentiate the actions of phenytoin.

*NSAIDs/Lithium/Probenecid/Cyclosporin*

Although not reported specifically with nimesulide, interactions between NSAIDs and lithium, probenecid and cyclosporin, have been documented. Caution is warranted if nimesulide is administered concurrently with any of these drugs.

**DOSAGE AND ADMINISTRATION**

The recommended daily dosage for adults and children over 14 is 100 mg bid, with plenty of fluid and preferably after meals. Mesulid is indicated for short-term therapy. The duration of treatment depends on the specific condition being treated but is usually between 3-14 days. For patients with osteoarthritis, short cycles of therapy for symptomatic relief are recommended.

**OVERDOSAGE**

A few cases of attempted overdose have been reported without signs of intoxication. Reported symptoms following overdose with other NSAIDs generally reflect the gastrointestinal, renal and CNS toxicities of NSAIDs. Should a patient ingest a large quantity of nimesulide, initiate symptomatic treatment including gastric lavage and restoration of water and electrolyte balance.

**PRESENTATION:** 30 caplets.

26/12/99 version 1