SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Mesulid® 100

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each caplet contains 100mg nimesulide.
Excipients with known effect: lactose, hydrogenated castor oil.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Off-white to light yellow capsule-shaped tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of acute pain.
Primary dysmenorrhoea.

Nimesulide should only be prescribed as second line treatment. The decision to prescribe nimesulide should be based on assessment of the individual patient's overall risks (see section 4.3 and 4.4).

4.2 Posology and method of administration

Mesulid should be used for the shortest possible duration, as required by the clinical situation. Moreover, undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms (see section 4.4).

The maximum duration of a treatment course with nimesulide is 15 days.

Adults:
One 100mg caplet twice a day after meals.

Elderly: in elderly patients there is no need to reduce the daily dosage (see section 5.2).

Children (< 12 years): Mesulid is contraindicated in these patients (see also section 4.3).

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

Impaired renal function: 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 Mesulid is contraindicated in case of severe renal impairment (creatinine clearance<30 ml/min) (see sections 4.3 and 5.2).

Hepatic impairment: the use of Mesulid is contraindicated in patients with hepatic impairment (see sections 4.3 and 5.2).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- 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.
- 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 (see sections 4.6 and 5.3).

4.4 Special warnings and precautions for use

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 acetylsalicylic acid, 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 acetylsalicylic acid (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

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.

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.

Cases of fixed drug eruption (FDE) have been reported with nimesulide.
Nimesulide should not be reintroduced in patients with history of nimesulide-related FDE (see section 4.8).

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 contains lactose, therefore patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Mesulid contains hydrogenated castor oil.
Mesulid contains less than 1 mmol sodium (23 mg) per caplet.

4.5 Interaction with other medicinal products and other forms of interaction

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 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. 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 cyclosporins.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy and Fertility:

The use of Mesulid is contraindicated in the third trimester of pregnancy (see section 4.3).

Like other NSAIDs, Mesulid is not recommended in women attempting to conceive (see section 4.4).

Inhibition of prostaglandin synthesis may have a negative impact on pregnancy and/or embryonic/fetal development. Results of epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after the use of an inhibitor of prostaglandin synthesis in the first stage of pregnancy. The absolute risk for cardiac malformations was increased from less than 1% to approximately 1.5%. The risk has been considered to increase with the dose and duration of treatment.

In animals, administration of inhibitors of prostaglandin synthesis has been shown to provoke an increase in pre- and post-implantation loss and in embryonic-fetal mortality. Furthermore, an increased incidence of various malformations, including the cardiovascular one, has been reported in animals to which inhibitors of prostaglandin synthesis were administered during the period of organogenesis.

Studies in rabbits have shown an atypical reproductive toxicity (see section 5.3) and no adequate data from the use of nimesulide-containing medicinal products in pregnant women are available.

Oligohydramnios/Neonatal Renal Impairment and Premature Constriction/ Closure of Ductus Arteriosus:

Use of NSAIDs, including Mesulid, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation.
Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some post-marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation.

Therefore, during the first and second trimesters of pregnancy, Mesulid should not be given unless clearly necessary.

If Mesulid is used by a woman who is trying to conceive, or during the first and second trimesters of pregnancy, the dose and duration of treatment should be kept as low as possible.

If NSAID treatment is necessary between about 20 weeks and 28 weeks gestation, consider ultrasound monitoring of amniotic fluid if Mesulid treatment extends beyond 5 days, and also consider antenatal monitoring for ductus arteriosus constriction after exposure to Mesulid for several days from gestational week 20 onward. Discontinue Mesulid if oligohydramnios or ductus arteriosus constriction occurs and follow up according to clinical practice.

During the third trimester of pregnancy, all inhibitors of prostaglandin synthesis may expose

- the fetus to:
  - cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
  - renal dysfunction (see above), which may progress to renal insufficiency with oligohydramnios;
- the mother and the newborn infant, at the end of pregnancy, to:
  - possible prolongation of bleeding time, and an antiplatelet effect which may occur even at very low doses;
  - inhibition of uterine contractions resulting in delay or prolongation of labour.

Consequently, Mesulid is contraindicated during the third trimester of pregnancy.

Breastfeeding:
It is not known whether nimesulide is excreted in human milk. Mesulid is contraindicated when breastfeeding (see sections 4.3 and 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a) General description

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) (see section 4.4).

Oedema, hypertension, and cardiac failure have been reported in association with NSAID treatment. Very rare cases of bullous reactions including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis have been reported.

The most commonly-observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4 - Special warnings and precautions for use) have been reported following administration. Less frequently, gastritis has been observed.

b) Table of adverse reactions

The following listing of undesirable effects is based on data from controlled clinical trials (approximately 7,800 patients) and from post marketing surveillance with reporting rates classified as: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), including isolated cases.

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* Gastrointestinal bleeding Duodenal ulcer and perforation Gastric ulcer and perforation
	Very rare	Gastritis* Abdominal pain Dyspepsia Stomatitis Melaena
Hepato-biliary disorders (see section 4.4."Special warnings and special precautions for use")	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

	Unknown	Fixed drug eruption (see Section 4.4)
Renal and urinary disorders	Rare	Dysuria* Haematuria*
	Very rare	Urinary retention* Renal failure Oliguria Interstitial nephritis
General disorders	Uncommon	Oedema*
	Rare	Malaise* Asthenia*
	Very rare	Hypothermia

*frequency based on clinical trial

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il/

4.9 Overdose

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. Anaphylactoid 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 haemodialysis, 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, haemodialysis, or haemoperfusion may not be useful due to high protein binding. Renal and hepatic function should be monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
ATC code: M01AX17

Nimesulide is a non-steroidal anti-inflammatory drug with analgesic and antipyretic properties which acts as an inhibitor of prostaglandin synthesis enzyme cyclo-oxygenase.

5.2 Pharmacokinetic properties

Nimesulide is well absorbed when given per o.s. 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. No statistically significant difference has been found between these figures and those seen after 100mg given twice daily for 7 days.

Up to 97.5% binds to plasma proteins.

Nimesulide is extensively metabolised 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 metabolised by CYP2C9 (see under section 4.5). 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. $T_{½}$ is between 3.2 and 6 hours.

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.

The kinetic profile of nimesulide was unchanged in the elderly after acute and repeated doses.

In an acute experimental study carried out in patients with mild to moderate renal impairment (creatinine clearance 30-80 ml/min) versus healthy volunteers, peak plasma levels of nimesulide and its main metabolite were not higher than in healthy volunteers. AUC and $t_{1/2}$ beta were 50% higher, but were always within the range of kinetic values observed with nimesulide in healthy volunteers. Repeated administration did not cause accumulation.
Nimesulide is contra-indicated in patients with hepatic impairment (see section 4.3).

5.3 Preclinical safety data

Preclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.
In repeated dose toxicity studies, nimesulide showed gastrointestinal, renal and hepatic toxicity.
In reproductive toxicity studies, embryotoxic and teratogenic effects (skeletal malformations, dilatation of cerebral ventricles) were observed in rabbits, but not in rats, at maternally non-toxic dose levels. In rats, increased mortality of offspring was observed in the early postnatal period and nimesulide showed adverse effects on fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose, cellulose microcrystalline, sodium starch glycolate, hydrogenated castor oil, docusate sodium, magnesium stearate, hydroxypropyl cellulose.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage
Store below 25°C.

6.5 Nature and contents of the container
Blister packs (10, 20, 30 caplets).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7. RESTRATION HOLDER

Rafa laboratories LTD., P. O. Box 450, Jerusalem 9100301
Registration number: 0682727431

Manufactured under license from Helsinn Healthcare SA, Switzerland.

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