APPROVED
The Order of Ministry of Health of Ukraine
23.10.2020 No. 2417
Registration certificate No. UA/7649/02/01

AMENDED
The Order of Ministry of Health of Ukraine
10.11.2023 No. 1946

INSTRUCTION
for medical use
NIMID®

Composition:
active substance: nimesulide;
1 tablet contains nimesulide 100 mg;
excipients: microcrystalline cellulose, croscarmellose sodium, magnesium stearate, silica colloidal anhydrous.

Pharmaceutical form. Tablets.
Basic physical and chemical properties: round light-yellow tablets, smooth on both sides.

Pharmacotherapeutic group. Anti-inflammatory and antirheumatic products, non-steroids. ATC code M01A X17.

Pharmacological properties.
Pharmacodynamics.
Nimesulide is a non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties which acts as an inhibitor of prostaglandin synthesis enzyme cyclooxygenase.
Pharmacokinetics.
Absorption.
Nimesulide is well absorbed when given by mouth. After a single dose of 100 mg nimesulide, a peak plasma level of 3–4 mg/l is reached in adults after 2–3 hours.
Area under the concentration-time curve (AUC) is 20–35 mg×h/l. No statistically significant difference has been found between these figures and those seen after 100 mg given twice daily for 7 days. Up to 97.5% of nimesulide binds to plasma proteins.
Biotransformation and elimination.
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 (see “Interaction with other medicinal products and other forms of interaction” section). 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. Half-life 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 feces.
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 half-life in patients with impaired renal function 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 contraindicated in patients with hepatic impairment (see "Contraindications" section).
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.

Clinical characteristics.
Indications.
Treatment of acute pain, primary dysmenorrhea.
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.

Contraindications.
Known hypersensitivity to nimesulide, to any other NSAID or to any of the excipients of the drug.
History of hyperergic reactions (e.g., bronchospasm, rhinitis, urticaria) in response to acetylsalicylic acid or other NSAIDs.
History of hepatotoxic reactions to nimesulide
Concomitant use of other substances with potential hepatotoxicity.
Alcoholism and drug addiction.
History of gastrointestinal bleedings or perforations associated with the previous use of NSAIDs.
Peptic ulcer in the acute phase, history of a bleeding in the digestive tract, ulcer, or perforation.
History of cerebrovascular bleedings or other bleedings, as well as diseases accompanied by bleeding.
Severe blood clotting disorders.
Severe heart failure.
Severe renal dysfunction.
Severe hepatic dysfunction.
Fever and/or flu-like symptoms.
Children under 12 years.
The third trimester of pregnancy and breastfeeding period (see "Use during pregnancy or breastfeeding" and "Preclinical safety data" sections).

Interaction with other medicinal products and other forms of interaction.
Pharmacodynamic interactions.
Corticosteroids. Corticosteroids may increase the risk of gastrointestinal ulceration or bleeding (see "Special warnings and precautions for use" section).

Antiplatelet agents and selective serotonin reuptake inhibitors (SSSRIs). Antiplatelet agents and selective serotonin reuptake inhibitors (SSSRIs) increase the risk of ulcer or bleeding in the digestive tract (see "Special warnings and precautions for use" section).
Anticoagulants. NSAIDs may enhance the effects of anticoagulants such as warfarin (see "Special warnings and precautions for use" section). 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 (see also "Special warnings and precautions for use" section) and is contraindicated in patients with severe coagulation disorders (see also "Contraindications" section). If the combination cannot be avoided, anticoagulant activity should be monitored closely.
Diuretics, angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin II antagonists (AIIA). NSAIDs may reduce the effect of diuretics and 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 cyclooxygenase 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 nimesulide 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 analyzed.
Other non-steroidal anti-inflammatory drugs (NSAIDs). The simultaneous use of nimesulide-containing medicinal products (see "Clinical characteristics" section) with other NSAIDs, including acetylsalicylic acid administered in anti-inflammatory doses (≥1 g as a single dose or ≥3 g as a daily total), is not recommended.
Pharmacokinetic interactions: effect of nimesulide on the pharmacokinetics of other drugs.
Furosemide. In healthy volunteers, nimesulide transiently reduces the effect of furosemide on the excretion of sodium and, to a lesser extent, on the excretion of potassium and reduces the diuretic response. Co-administration of nimesulide and furosemide leads to a reduction in area under the concentration-time curve (AUC) (about 20%) and total furosemide excretion without compromising renal clearance of the latter. Concomitant use of furosemide and nimesulide-containing medicinal products requires caution in patients with kidney or heart pathology (see "Special warnings and precautions for use" section).
Lithium. It has been reported that NSAIDs reduce the clearance of lithium, and this leads to high plasma levels and lithium toxicity. If nimesulide is prescribed for a patient taking lithium, lithium levels should be closely monitored.
Pharmacokinetic interactions: effects of other drugs on the pharmacokinetics of nimesulide.
In vitro studies have shown that tolbutamide, salicylic acid and valproic acid displace nimesulide from binding sites. However, despite a possible effect on nimesulide plasma levels, these interactions were not clinically significant.
Other interactions.
Potential pharmacokinetic interactions with glibenclamide, theophylline, warfarin, digoxin, cimetidine and an antacid preparation (a combination of aluminium and magnesium hydroxide) have also been studied *in vivo*. No clinically significant interactions were noted.
Nimesulide inhibits CYP2C9. The plasma concentrations of drugs that are metabolized by this enzyme may be increased if co-administered with Nimid®. Caution is required when nimesulide is taken less than 24 hours before or after treatment with methotrexate because the serum levels of methotrexate may increase and thus the toxicity of this drug may be greater.
Given their effect on renal prostaglandins, prostaglandin synthetase inhibitors such as nimesulide may increase the nephrotoxicity of cyclosporines.

Special warnings and precautions for use.

Side effects can be minimized by using the lowest effective dose for the shortest time necessary to control symptoms (see "Posology and method of administration" section and gastrointestinal and cardiovascular risks below).

Suspend treatment if benefits are not observed.

The use of nimesulide should be avoided concurrently with NSAIDs, including selective inhibitors of cyclooxygenase-2. In addition, during Nimid® therapy patients should be advised to refrain from taking other analgesics concomitantly.

Concomitant administration with known hepatotoxic drugs, and alcohol abuse must be avoided during treatment with nimesulide.

NSAIDs may mask the fever related to an underlying bacterial infection.

Effects on the liver.

In rare cases an association between nimesulide and serious liver reactions has been reported, including some very rare fatal cases (see also "Adverse reactions" section). Patients who experience symptoms consistent with liver damage during treatment with nimesulide (e.g., anorexia, nausea, vomiting, abdominal pain, fatigue, dark urine) or who have abnormal liver function tests during treatment should discontinue treatment. These patients should no longer use nimesulide.

Liver damage, reversible in most cases, was reported after short exposure to the drug.

When patients taking nimesulide develop a fever and/or flu-like symptoms, treatment should be discontinued.

Gastrointestinal effects.

During treatment with all NSAIDs, at any time with or without warning symptoms or previous history of severe gastrointestinal events, GI bleeding, or ulceration/perforation which may be fatal have been reported. The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing doses of NSAIDs in patients with a history of ulcers, particularly when complicated by hemorrhage or perforation (see "Contraindications" section) and in the elderly. These patients should begin treatment with the lowest available dose. Combination therapy with protective agents (e.g., misoprostol or proton pump inhibitors) should be considered for these patients and also for those who require simultaneous taking of low doses of acetylsalicylic acid or other drugs that may increase the risk of gastrointestinal events (see below and "Interaction with other medicinal products and other forms of interaction" section).

Patients with a history of gastrointestinal toxicity, especially if elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding), especially in early treatment.

At any time during treatment bleeding, gastrointestinal ulcers/perforation with or without warning symptoms or previous gastrointestinal events may appear. If gastrointestinal bleeding or ulcers appear, treatment with nimesulide should be discontinued.

Nimesulide should be used with caution in patients with gastrointestinal diseases, including previous peptic ulcer, gastrointestinal bleeding, ulcerative colitis or Crohn's disease (see "Adverse reactions" section).

Caution should be recommended for patients taking medications simultaneously that may increase the risk of ulceration or bleeding, like oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors (SSRIs), or antiplatelet agents such as acetylsalicylic acid.

When there is bleeding or gastrointestinal ulceration in patients taking nimesulide the treatment should be discontinued.

NSAIDs should be administered with caution in patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see "Adverse reactions" section). Simultaneous use of nimesulide with other drugs, such as oral contraceptives, anticoagulants, antiaggregants, can cause exacerbation of Crohn's disease and other diseases of the digestive tract.

Cardiovascular and cerebrovascular effects.

Adequate monitoring and appropriate instructions are necessary for patients with a history of hypertension and/or mild to moderate congestive heart failure because fluid retention and edema have been reported in association with NSAID treatment.

Clinical and epidemiological data suggest that the use of some NSAIDs (particularly at high doses and long-term treatment) may be associated with a modest increased risk of arterial thrombotic events (e.g., myocardial infarction or stroke). There is insufficient data to exclude this risk with nimesulide.
Patients with uncontrolled hypertension, congestive heart failure, ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease must be treated with nimesulide only after careful consideration. Similar considerations must be made before starting long-term treatment in patients with risk factors for cardiovascular disease (e.g., hypertension, hyperlipidemia, diabetes mellitus, smoking).
Since nimesulide can interfere with platelet function, it should be used with caution in patients with bleeding diathesis (see also "Contraindications" section). However, Nimid® is not a substitute for acetylsalicylic acid for cardiovascular prophylaxis.
Renal effects.
Caution should be used in the treatment of patients with renal or cardiac insufficiency with nimesulide as it may impair renal function. In this case, treatment should be discontinued (see also "Interaction with other medicinal products and other forms of interaction" section).
Elderly.
Elderly patients have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation, which can be fatal (see "Adverse reactions" section), as well as impaired kidney, heart and liver function. Consequently, appropriate clinical monitoring is recommended.
Skin effects.
Severe 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 "Adverse reactions" section). Patients appear to be at increased risk early in treatment. The onset of the reaction occurs in most cases within the first month of treatment. Nimesulide 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. Treatment with nimesulide should not be resumed in patients with a history of nimesulide-related FDE (see "Adverse reactions" section).
Effects on fertility.
The use of Nimid® may compromise female fertility and is not recommended for women trying to get pregnant. In women who have difficulty conceiving or who are being evaluated for infertility, consider stopping treatment with Nimid® (see "Pregnancy and breastfeeding" section).
Excipients.
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially sodium-free.

Pregnancy and breastfeeding.
Pregnancy.
The use of nimesulide is contraindicated in the third trimester of pregnancy (see "Contraindications" section).
Inhibition of prostaglandin synthesis may have a negative impact on pregnancy and/or developing embryo/fetus. Results of epidemiological studies suggest a higher risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk of cardiac malformations was increased from less than 1% up to about 1.5%. It is believed that the risk increases with dose and duration of therapy.
In animals, the administration of prostaglandin synthesis inhibitors has been shown to cause increased pre- and post-implantation loss and embryo/fetal mortality. In addition, an increased incidence of various malformations, including cardiovascular malformation, has been reported in

animals that were administered prostaglandin synthesis inhibitors during the period of organogenesis.
From the 20th week of pregnancy onwards, the use of nimesulide may cause oligohydramnios resulting from fetal renal dysfunction. This condition may occur shortly after initiation of treatment and is usually reversible upon discontinuation of treatment. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment discontinuation. Therefore, nimesulide should not be administered during the first and second trimester of pregnancy unless clearly necessary. If nimesulide is used by a woman attempting to conceive, or during the first or second trimester of pregnancy, the dose should be kept as low as possible and the duration of treatment as short as possible. Following exposure to nimesulide for several days from gestational week 20 onwards, prenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered. Nimesulide should be discontinued in pregnant women if oligohydramnios or ductus arteriosus constriction are found.
During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the fetus to:
- pneumocardial toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligohydroamnios (see above);
The mother and neonate at the end of pregnancy may experience:
- a possible prolongation of bleeding time and an anti-platelet aggregation effect which can occur even at very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour.
Breastfeeding.
It is not known whether nimesulide is excreted into human milk. Nimesulide is contraindicated in women who are breastfeeding (see “Contraindications” and “Preclinical safety data” sections).
Fertility.
As with other NSAIDs, the use of nimesulide-containing medicinal products is not recommended in women attempting to become pregnant (see “Special warnings and precautions for use” section). In women who have difficulty conceiving or who are being evaluated for infertility, consider stopping treatment with nimesulide.
If pregnancy is established during the use of nimesulide, the doctor should be informed about it.

Effects on ability to drive vehicles and use machinery.
There have been no studies on the effect of nimesulide-containing medicinal products on the ability to drive and use machines. However, patients suffering from dizziness, vertigo, or drowsiness after taking nimesulide should refrain from driving or operating machinery.

Posology and method of administration.
In order to reduce the frequency of adverse reactions, it is necessary to use the minimum effective dose for the shortest time necessary to control symptoms (see “Special warnings and precautions for use” section). The maximum duration of a treatment cycle with nimesulide is 15 days.
Adults. 1 tablet (100 mg of nimesulide) twice daily after meals.
Elderly. It is not necessary to reduce the daily dose for elderly patients (see “Pharmacokinetics” section).
Children. Nimesulide-containing medicinal products are contraindicated for children under 12 years (see also “Contraindications” section). Based on the kinetic profile in adults and the pharmacodynamic characteristics of nimesulide, no dosage adjustment is necessary in children aged 12–18 years.
Renal insufficiency. Based on the pharmacokinetics there is no need to adjust the dose in patients with mild to moderate renal insufficiency (creatinine clearance 30–80 ml/min); Nimid® is contraindicated in the case of severe renal impairment (creatinine clearance <30 ml/min) (see “Contraindications” and “Pharmacokinetics” sections).

Hepatic impairment. The use of Nimid® is contraindicated in patients with hepatic impairment (see "Pharmacokinetics" section). Side effects can be minimized by using the lowest effective dose for the shortest time necessary to control symptoms (see "Special warnings and precautions for use" section).

Children.
Nimid® is contraindicated for children under 12 years.

Overdose.
The symptoms associated with acute NSAID overdose are usually limited to apathy, drowsiness, nausea, vomiting and epigastric pain, generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory failure and coma may occur also, albeit rarely. Anaphylactic reactions have been reported after ingestion of therapeutic doses of NSAIDs and may manifest after overdose as well. In case of overdosage with NSAIDs, patients must be managed with symptomatic and supportive treatment. There are no specific antidotes. No information is available on the elimination of nimesulide by means of hemodialysis: given its high degree of protein binding (up to 97.5%), dialysis is unlikely to be useful in the treatment of overdose. Vomiting and/or activated charcoal (60 to 100 g in adults) and/or osmotic cathartics may be indicated, if administered within 4 hours in patients with symptoms of overdose or who have taken large doses of nimesulide. Forced diuresis, alkalinization of urine, hemodialysis or hemoperfusion may not be useful because of the high protein binding. Renal and hepatic function must be monitored.

Adverse reactions.
The following listing of undesirable effects is based on data from controlled clinical trials* and from post marketing surveillance with reporting rates classified as: very common (>1/10); common (>1/100, <1/10), uncommon (>1/1000, <1/100); rare (>1/10000, <1/1000); very rare (<1/10000), including isolated cases; not known (frequency cannot be estimated from available data).

Blood and lymphatic system 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*, nightmares*
Nervous system disorders	Uncommon	Dizziness*
	Very rare	Headache, drowsiness, encephalopathy (Reye's syndrome)
Eye disorders	Rare	Blurred vision*
	Very rare	Visual disturbances
Ear and labyrinth disorders	Very rare	Vertigo (dizziness)
Cardiac disorders	Rare	Tachycardia*
Vascular disorders	Uncommon	Hypertension*
	Rare	Hemorrhage*, fluctuations in blood pressure*, hot flashes*
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnea*
	Very rare	Asthma, bronchospasm
Gastrointestinal disorders	Common	Diarrhea*, nausea*, vomiting*
	Uncommon	Constipation*, flatulence*, gastrointestinal bleeding, duodenal/gastric ulcer and perforation

	Very rare	Gastritis*, abdominal pain, dyspepsia, stomatitis, melena
Hepatobiliary disorders (see "Special warnings and precautions for use" section)	Common	Increased liver enzymes levels*
	Very rare	Hepatitis; fulminant hepatitis (including fatal cases), jaundice, cholestasis
Skin and subcutaneous tissue disorders	Uncommon	Pruritus*, eruptions*, increased sweating*
	Rare	Erythema*, dermatitis*
	Very rare	Urticaria, angioedema, facial edema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
	Not known	Fixed drug eruption (see "Special warnings and precautions for use" section)
Renal and urinary disorders	Rare	Dysuria*, hematuria*
	Very rare	Urinary retention*, renal insufficiency, oliguria, interstitial nephritis
Systemic disorders and conditions related to the administration site	Uncommon	Edema*
	Rare	Malaise*, asthenia*
	Very rare	Hypothermia
* Frequency based on clinical trial		

The most commonly observed adverse events are gastrointestinal. Patients may experience peptic ulcers, perforation or gastrointestinal hemorrhage, sometimes fatal, particularly in the elderly (see "Special warnings and precautions for use" section). After the administration of nimesulide containing medicinal products the following have been reported: nausea, vomiting, diarrhea, flatulence, constipation, dyspepsia, abdominal pain, melena, hematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see "Special warnings and precautions for use" section). Gastritis has been observed less frequently. Edema, hypertension and heart failure have been reported in association with NSAID treatment. Very rare cases of reactions involving bullous lesions including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. Clinical and epidemiological studies suggest that the use of some NSAIDs (particularly at high doses and for long-term treatment) may be associated with a modest increased risk of arterial thrombotic events (e.g., myocardial infarction or stroke) (see "Special warnings and precautions for use" section).

Reporting of suspected adverse reactions.

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Medical and pharmaceutical workers, as well as patients or their legal representatives are asked to report any suspected adverse reactions and lack of effectiveness of the medicinal product through the Pharmacovigilance Automated Information System at: https://aisf.dec.gov.ua.

Shelf life. 4 years.

Storage conditions.
Store at the temperature below 25ºC in original package.
Keep out of reach of children.

Package.
10 tablets in a blister, 1 blister in a cardboard package No. 10 (10×1).
10 tablets in a blister, 1 blister in a cardboard package, 10 packages in a box No. 100 (10×1×10).

Conditions of supply.
By prescription.

Manufacturer.
KUSUM HEALTHCARE PVT LTD.

Location of manufacturer and its address of business activity.
SP-289 (A), RIICO Industrial area, Chopanki, Bhiwadi, Dist. Alwar (Rajasthan), India.

Date of last revision.