SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NOVO-PLAN 1 g/2 ml Solution for I.M/I.V Injection
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:
Metamizol Sodium 1.000 mg

Excipients:
See section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Ampoule.
Clear, almost colorless to yellow solution, practically particle-free.

4. CLINICAL PARTICULARS

4.1 Therapeutical indications

Severe or resistant pain and fever.

4.2 Posology and method of administration

Posology/Frequency and Duration of administration:
If the doctor has no other suggestions, the doses reported below are applied.

Intravenous or intramuscular administration is recommended when rapid analgesic effect is required or when oral or rectal administration is not indicated.

Adults and teens aged 15 years old and over:
One-time dose to be administered intravenously or intramuscularly is 2-5 ml. These one-time doses can be increased to a maximum daily dose of 10 ml (5 g).

Method of administration:
Administered as intramuscularly and intravenously.

NOVO-PLAN must be used with the advice of a physician. Intravenous administration should be done under the control of a physician.

These reported one-time doses can be repeated up to 4 times a day.

Warnings for use:
Necessary precautions should be taken for shock treatment, and the injection solution should be applied after it is brought to body temperature.

The most common reason for the emergence of severe blood pressure and shock state is the rapid injections. For this reason, intravenous injections against sudden drop in blood pressure should be done very slowly, not exceeding 1 ml per minute provided that the blood pressure, pulse and breathing are kept under control while the patient is lying down. Metalizole doses above 1 g should only be used if there is a definite indication, as the non-allergic low blood pressure may be dose dependent.
NOVO-PLAN injection solution should not be mixed with other drugs in the same injector.

Additional information on special populations:
Renal/Liver failure:
In patients with kidney or liver disorders, high doses should be avoided as the elimination rate of metamizole decreases. However, the dose does not need to be reduced for short-term treatment. There is insufficient experience gained in long-term treatment in patients with kidney or liver failure.

Pediatric population:
Unless medical obligation, NOVO-PLAN should not be applied to babies less than 3 months old or weighing less than 5 kg. In children under one year old, NOVO-PLAN should only be administered intramuscularly.

A one-time dose in a child weighing about 30 kg is 0.4 to 1 ml.

In those with a lower or higher body weight, the dose is suitably reduced or increased.

The dosage schedule below may be guiding.

Body weight	i.m. (single dose)	i.v. (single dose)	Maximum dose/day
3-11 months (5-8 kg)	0,1-0,2 ml	-	0,4 g
1-3 years (9-15 kg)	0,2-0,5 ml	0,2-0,5 ml	1,0 g
4-6 years (16-23 kg)	0,3-0,8 ml	0,3-0,8 ml	1,6 g
7-9 years (24-30 kg)	0,4-1,0 ml	0,4-1,0 ml	2,0 g
10-12 years (31-45 kg)	0,5-1,5 ml	0,5-1,5 ml	3,0 g
13-14 years (46-53 kg)	0,8-1,8 ml	0,8-1,8 ml	3,6 g

Geriatric population:
Possible impairments in kidney and liver function should be considered in elderly patients and patients with a general condition.

4.3. Contraindications

- Allergy to metamizole or other pyrazolones (eg phenazone, propyphenazone) or pyrazolidines (eg phenylbutazone, oxyphenbutazone), eg. agranulocytosis previously developed against one of these substances
- Impaired bone marrow function (eg caused by cytostatic therapy) or hematopoietic system diseases
- Patients who develop bronchospasm or other anaphylactoid reactions (eg urticaria, rhinitis, angioedema) against analgesics such as salicylates, paracetamol, diclofenac, ibuprofen, indomethacin, naproxen.
- Allergy to one of the excipients of NOVO-PLAN

- Acute intermittent hepatic porphyria (risk of induction of porphyria attacks)
- Congenital glucose -6-phosphate dehydrogenase deficiency (risk of hemolysis)
- Babies under 3 months old or weighing less than 5 kg

NOVO-PLAN should not be administered intravenously in infants between 3 and 11 months.

NOVO-PLAN should not be administered parenterally in patients with unstable hemodynamics and/or hypotension.

Pregnancy and breastfeeding (see section 4.6)

4.4 Special warnings and precautions for use

Metamizole-induced agranulocytosis is an event of at least a week of immuno-allergic origin. These reactions are very rare but can be severe and life threatening and can result in death. These are not dose-dependent and can occur at any time during treatment.

All patients should be warned that they should immediately stop taking the medication and consult their doctor if any of the following signs or symptoms, possibly related to neutropenia, occur: fever, chills, sore throat, ulceration in the oral cavity. In the case of neutropenia (<1,500 neutrophils / mm3), treatment should be discontinued immediately and complete blood count should be checked urgently and monitored to return to normal values.

Pancytopenia: If pancytopenia occurs, treatment should be discontinued immediately and follow-up with complete blood count until blood values return to normal.
All patients should be warned to seek medical attention immediately if signs and symptoms (such as general malaise, infection, fever, bruises, bleeding, paleness) that may be indicative of blood dyscrasia during metamizole use.

Anaphylactic shock: This type of reaction occurs mainly in sensitive patients. Therefore, metamizole should be prescribed with caution in asthmatic or atopic patients (see section 4.3 "Contraindications").

Severe skin reactions: Life-threatening skin reactions such as Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported during metamizole use. If the signs or symptoms of SJS or TEN (usually blistering blisters or mucous lesions accompanied by an increasingly severe skin rash) develop, metamizole treatment should be discontinued immediately and never re-administered. Patients should be informed about signs and symptoms and should be followed closely for skin reactions, especially in the first weeks of treatment.

Anaphylactic/Anaphylactoid reactions
When choosing the route of administration, it should be considered that parenteral administration carries a higher risk for anaphylactic/anaphylactoid reactions.

In particular, the following patients are at particular risk of potential severe anaphylactoid reactions to metamizole (see section 4.3 "Contraindications"):

- Patients with bronchial asthma; especially those with rhinosinusitis polyposis at the same time
- Patients with chronic urticaria

- Patients with alcohol intolerance; that is, patients who react even to a small amount of certain alcoholic beverages with symptoms such as runny nose, lacrimation and pronounced redness.
- Alcohol intolerance can be an indicator of undiagnosed analgesic asthma syndrome.
- Patients with intolerance to dyes (eg tartrazine) or preservatives (eg benzoates)
- Patients should be carefully questioned before applying NOVO-PLAN. In patients who are found to be at special risk for anaphylactoid reactions, NOVO-PLAN should be administered after careful consideration of possible risks and expected benefit. If NOVO-PLAN is to be used under these conditions, strict medical supervision is required and the conditions for emergency treatment should be available.

If anaphylactic shock occurs, the following measures should be taken. The injection is stopped immediately when the first symptoms such as sweating, nausea and cyanosis appear. Along with other usual measures, the patient is laid down with his head down and the airway is kept open.

Medicines to be applied immediately:
i.v. adrenaline (epinephrine): For this, 1 ml of a commercially available 1/1000 epinephrine solution is diluted to 10 ml, and 1 ml (0.1 mg of epinephrine) is injected slowly by checking the pulse and blood pressure (attention to heart rhythm disturbances!). If necessary, epinephrine injections may be repeated.

Then i.v. glucocorticoids, for example 250-1000 mg methylprednisolone, are administered via the route. These doses are recommended for a normal weight adult. In children, dose reduction associated with body weight should be made. These doses can be repeated if necessary.

Following this, plasma expander Human Albumin, i.v. with solutions such as full electrolyte solution. volume substitution is made from the road.

Other treatment methods: Artificial respiration, oxygen inhalation and antihistamines.

Isolated hypotensive reactions
Metamizole administration may cause isolated hypotensive reactions (see section 4.8). These reactions are probably dose-dependent and tend to occur more often after parenteral administration. Things to consider in order to prevent such severe hypotensive reactions in the following situations:

• Intravenous injection should be applied slowly.
• Previously impaired hemodynamics with existing hypotension; patients with loss of volume and dehydration, patients with poor circulation or initial circulatory failure, and
• Caution should be exercised in patients with high fever.

In such patients, the indication for metamizole should be determined with a special sensitivity; If NOVO-PLAN is to be applied under these conditions, strict medical supervision is required. Protective measures (stabilization of hemodynamics) may be necessary to reduce the risk of hypotensive reaction. For patients with hypotension or unstable circulation, see the "Contraindications" section.

Metamizole should only be used under close hemodynamic monitoring in patients who need to avoid lowering blood pressure, such as patients with severe coronary heart disease or blood vessel stenoses that nourish the brain.

In patients with kidney or liver disorders, it is recommended to avoid high doses of metamizole, since the elimination rate of metamizole decreases in these patients.

Intravenous injection should be administered very slowly (should not exceed 1 ml per minute) to ensure that the injection can be stopped when the first sign of anaphylactic / anaphylactoid reaction is seen (see section 4.8) and to minimize the risk of isolated hypotensive reactions.

4.5 Interactions with other medical products and other forms of interaction
When used with cyclosporine, it can lower cyclosporin levels. Therefore, regular checks are required.

Severe hypothermia may occur when NOVO-PLAN is used with chlorpromazine.

It is known that there may be interactions between pyrazolones and oral anticoagulants, captopril, lithium, methotrexate and triamterene, and that the effectiveness of antihypertensives and diuretics may change in combined use. It is not known to what extent metamizole causes these interactions.

Adding metamizole to methotrexate may increase the hematotoxicity of methotrexate, especially in elderly patients. Therefore, this combination should be avoided.

NOVO-PLAN can be dissolved in 5% glucose, 0.9% NaCl or ringer lactate solution. However, these solutions should be applied immediately as their stability is limited.

Due to the possibility of incompatibility, metamizole sodium should not be administered with other injectable drugs.

Metamizole may reduce the effect of acetylsalicylic acid (aspirin) on platelet aggregation when taken simultaneously. Therefore, this combination should be used with caution in patients using low-dose aspirin for cardioprotection.

Metamizole bupropion can cause low blood concentrations. For this reason, caution is recommended in the simultaneous use of metamizole and bupropion.

4.6 Pregnancy and lactation
General advice
Pregnancy category: C

Women with childbearing potential/Contraception
Women with childbearing potential must have effective contraception during treatment.

Pregnancy
Metamizole passes into the placenta. There is no evidence that the drug is harmful to the fetus. Metamizole did not show teratogenic effects in rats and rabbits, and high doses of fetotoxicity were observed, which were only maternally toxic. However, clinical data on the use of NOVO-PLAN during pregnancy are still insufficient.

That is why it is recommended not to use NOVO-PLAN in the first trimester of pregnancy. In the three months that follow, only potential benefit and risk are used after a careful weighing by a doctor.

However, NOVO-PLAN should not be used in the last three months of pregnancy. Because, although metamizole is only a weak prostaglandin synthesis inhibitor, the possibility of perinatal complications arising due to premature closure of the ductus arteriosus and deterioration in both maternal and neonatal platelet aggregability cannot be excluded.

Lactation
Metamizole metabolites pass into breast milk. Breastfeeding should be avoided during the application of NOVO-PLAN and for the next 48 hours.

The reproductive capability/Fertility
Metamizole metabolites pass into breast milk. Breastfeeding should be avoided during the application of NOVO-PLAN and for the next 48 hours.

4.7 Effects on ability to drive and use machines
There are no known adverse effects on concentration and reaction ability within the recommended dosage limits. However, it should be kept in mind that, at least in high doses, concentration and reaction ability may be impaired and a risk may arise where this ability is of particular importance (eg driving a vehicle or using machinery) (especially if alcohol use is involved).

4.8 Undesirable effects

Adverse drug reactions are specified according to the following frequencies::
Very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10.000 and <1/1000), very rare (<1/10.000) and unknown (estimation based on the existing data is impossible).

Blood and lymphatic system diseases
Rare: Death-induced pancytopenia, aplastic anemia, agranulocytosis and leukopenia.
Very rare: Thrombocytopenia

These reactions are considered to be of immunological origin. These may still occur even though NOVO-PLAN has been used many times without any complications.

Typical symptoms of agranulocytosis are inflammatory mucosal lesions (eg oropharyngeal, anorectal, genital), sore throat, fever (sometimes even unexpectedly persistent or recurrent fever). However, typical symptoms of agranulocytosis in patients undergoing antibiotic therapy may be minimal.

The erythrocyte sedimentation rate has increased greatly, and the lymph nodes have typically grown slightly, or there is no growth.

Typical symptoms of thrombocytopenia are petechiae on the skin and mucous membranes with an increased tendency to bleeding.

Immune system diseases
Anaphylactic / anaphylactoid reactions

Rare: Metamizole can cause anaphylactic / anaphylactoid reactions.
Very rare: These reactions can become severe and life threatening and sometimes result in death. These reactions may occur even if the NOVO-PLAN has been used many times without causing any complaints.

Such reactions are; It can occur immediately after the administration of metamizole or after hours. But the usual situation here; reaction occurs within the first hour after application.

Moderate anaphylactic / anaphylactoid reactions typically occur as cutaneous and mucosal symptoms (itching, burning, flushing, urticaria, blisters), dyspnea, and less often gastrointestinal complaints.

Mild reactions can progress to severe forms with generalized urticaria, severe angioedema (including even larynx), severe bronchospasm, cardiac arrhythmias, drop in blood pressure (sometimes with increased blood pressure beforehand) and circulatory shock over time.
In patients with analgesic asthma syndrome, these intolerance reactions typically appear as asthma attacks

Cardiac diseases
Unknown: Kounis syndrome

Vascular diseases
Unknown: Isolated hypotensive reactions
Occasionally, temporarily isolated hypotensive reactions may occur during or after application (possibly without pharmacological origin and other signs of anaphylactic/anaphylactoid reaction), and in rare cases this reaction may take the form of a critical drop in blood pressure. Rapid injection may increase the risk of such a hypotensive reaction.

Skin and subcutaneous tissue disorders
Rare: Maculopapuleous rash.
Very rare: Stevens-Johnson syndrome or Lyell syndrome, circulatory shock.
Frequency not known: Besides cutaneous and mucosal anaphylactic/anaphylactoid manifestations mentioned above, occasional fixed drug eruptions (see section 4.4).

Kidney and urinary diseases
Very rare: Especially in patients with a history of kidney disease, kidney function may deteriorate acutely (acute renal failure), acute interstitial nephritis and in some cases, oliguria, anuria or proteinuria may occur.

Sometimes red coloring was observed in the urine; this may be due to a low concentration metabolite (rubazonic acid).

General disorders and diseases related to the application site
Pain and local reactions may occur at the injection site. Sometimes phlebitis can be added to the table.

4.9. Overdose and therapy

Symptoms:

Nausea, vomiting, abdominal pain, impaired renal function/acute renal failure (due to interstitial nephritis) and, more rarely, central nervous system symptoms (dizziness, somnolence, coma, convulsions), drop in blood pressure (sometimes shock) and cardiac arrhythmias (tachycardia) have been reported. After very high doses, urine may turn red as a result of the excretion of a harmless metabolite (rubazonic acid).

Treatment:

Metamizole has no known specific antidote. If the drug has been recently taken, primary detoxification (eg gastric lavage) or absorption reduction (eg activated charcoal) measures may be taken to limit further systemic absorption of the active ingredients. The main metabolite of the drug (4-N-methylaminoantipirin) can be eliminated by hemodialysis, hemofiltration, hemoperfusion or plasma filtration.

5. PHARMACOLOGIC PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic class: Pyrazolones

ATC code: N02BB02

Metamizole has analgesic, antipyretic and antispasmodic effects. Metamizole most likely has a combined central and peripheral form of action. Central mechanisms of action at the level of afferent lifter, spinal cord and periacuaductal gray matter may contribute to the analgesic effect of metamizole.

Its mechanism of action is not entirely clear. Some data suggests that metamizole and its main metabolite (4-Nmethylaminoantipirin) may have a combined central and peripheral effect model.

5.2 Pharmacokinetic properties

The pharmacokinetics of metamizole and its metabolites are not completely clear. But the following information can be given:

<u>Absorption:</u>

After oral administration, metamizole is fully hydrolyzed to its active metabolite, 4-N-methylaminoantipyrin (MAA). The absolute bioavailability of MAA is approximately 90% and slightly higher than after intravenous administration after oral administration. When metamizole is taken with nutrients, the pharmacokinetics of MAA does not change significantly.

<u>Biotransformation:</u>

The clinical effect is mainly MAA and to some extent 4-aminoantipyrin (AA). AA's AUC values make up about 25% of the MAA's AUC. Metabolites such as 4-N-acetylaminoantipirin (AAA) and 4-N-formylaminoantipyrin (FAA) appear to have no clinical effects. A nonlinear pharmacokinetic is observed for all metabolites. More studies are needed to make a judgment about the clinical significance of this finding. In short-term treatment, the accumulation of metabolites has little clinical significance.

Distribution:
Protein binding levels are 58% for MAA, 48% for AA, 18% for FAA and 14% for AAA. The plasma half-life of metamizole after an intravenous dose is about 14 minutes.

Elimination:
Approximately 96% of the radioactive intravenous dose is excreted in the urine and about 6% in the faeces. After a single oral dose, 85% of metabolites are excreted in the urine and this consist of 3% ± 1% of this is MAA, 6% ± 3% AA, 26% ± 8% AAA and 23% ± 4% FAA. After a single oral dose of metamizole of 1 g, renal clearance is 5 ml ± 2 ml/min for MAA, 38 ml ± 13 ml/min for AA, 61 ml ± 8 ml/min for AAA and 49 ml ± for FAA 5 ml/min. Plasma half-lives after the same dose are 2.7 ± 0.5 hours for MAA, 3.7 ± 1.3 hours for AA, 9.5 ± 1.5 hours for AAA and 11.2 ± 1.5 hours for FAA.

Linearity/nonlinear state:
A nonlinear pharmacokinetic is observed for all metabolites. More studies are needed to make a judgment about the clinical significance of this finding.

Characteristic features in patients
Geriatric population:
Drug exposure (AUC) increases 2-3 times in the elderly.

Liver failure:
In patients with liver cirrhosis, after a single dose of oral administration, the half-life of MAA and FAA increased 3-fold (10 hours), but the increase in AA and AAA was not so obvious.

Kidney failure:
Sufficient intensity studies have not been performed on patients with impaired kidney function.
The available data show that elimination is reduced for some metabolites (AAA and FAA).

5.3 Preclinical safety data
Acute toxicity
The lowest lethal doses of metamizole in mice and rats: approximately 4000 mg/kg body weight orally; approximately 2300 mg metamizole / kg body weight or 400 mg MAA/kg body weight intravenously. Intoxication symptoms were tachypnea, sedation, and premortal convulsions.

Chronic toxicity
Administration of metamizole at doses of 150 mg / kg body weight daily in rats and 50 mg/kg body weight daily in dogs was tolerated for 4 weeks.
Subchronic and chronic toxicity studies have been conducted in different animal species.
Metamizole was administered in rats at a dose of 100-900 mg/kg body weight daily for 6 months. At the highest dose (900 mg/kg), an increase in reticulocytes and Heinz bodies was detected after 13 weeks.

Metamizole was administered in dogs at doses of 30-600 mg/kg body weight daily for 6 months. From doses of 300 mg / kg per day, dose-related hemolytic anemia and impaired kidney and liver function have been observed. Higher doses caused changes in serum chemistry in both sexes and hemosiderosis in the liver and spleen; Also, bone marrow toxicity and anemia symptoms were detected.

In vitro and *in vivo* experiments gave conflicting results for metamizole in the same test systems.

Carcinogenicity
No long-term studies in rats showed any evidence of carcinogenic potential. In two of the three long-term studies, an increase in liver cell adenomas at high doses has been reported.

Mutagenicity
Both positive and negative results have been described in the literature. However, in-vitro and in-vivo studies with Hoechst grade material indicated did not show any evidence of mutagenic potential.

Reproductive toxicity
No teratogenic potential has been demonstrated in embryotoxicity studies in rats and rabbits. Lethal effects have been reported in rabbits at a dose of 100 mg / kg / day without maternal toxicity.

Fatal embryotoxic effects in rats, maternal toxicity occurred in the observed dose range. Doses above 100 mg/kg/day in rats caused an increase in mortality in the offspring, along with prolongation in gestation and impaired birth.

In fertility tests, a slight decrease in the pregnancy rate of the generation giving birth at doses above 250 mg/kg/day was shown. Fertility of F1 generation is not affected.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Injectable distilled water

6.2. Incompatibilities
Not applicable.

6.3. Shelf life
24 months.

6.4. Special precautions for storage
It should not be used after the expiration date printed on the package.
Store at room temperature under 25°C.

6.5. Nature and contents of container
NOVO-PLAN: Packed as 2mlx 10 ampoule, 2ml x 50 ampoule and 2ml x 100 ampoule.

6.6 Special precautions for and other handling
Unused products or waste materials must be disposed of in accordance with the “Regulation Related to the Control of Medical Wastes” and “Regulation Related to the Control of Packaging Materials and Packaging Waste”.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER(S)

139/44

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

First licence date: 09.07.1986
Licence revision date:

10. DATE OF REVISION OF THE TEXT

19.09.2019