SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
DEVALJIN 1 g/2 ml I.M/I.V ampoules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substance:
Metamizole sodium.....1000 mg

Excipient(s):
Sodium metabisulfite.....1.4 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection.
Almost colourless to yellow, odourless, clear solution.

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
Severe or persistent pain and fever.

4.2. Posology and method of administration
Posology/frequency and duration of administration:
If there is no other recommendation of the doctor, the following doses 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 young people aged 15 and over:
One-time dose to be administered intravenously or intramuscularly is 2-5 ml. These one-time doses can be increased up to a maximum daily dose of 10 ml (5 g).

Method of administration:
It is administered intramuscularly and intravenously.

DEVALJIN ampoule must be used with the advice of a physician. Intravenous administration should be performed under the supervision of a physician.

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

Warnings on the method of use:

Necessary precautions should be taken for the treatment of shock, and the injection solution should be administered after it is brought to body temperature.
The most common cause of severe low blood pressure and shock is the rapid administration of injections. For this reason, intravenous injections against sudden drop in blood pressure should be performed very slowly, not exceeding 1 ml per minute, while the patient is lying down, provided that blood pressure, pulse and respiration are kept under control. Since non-allergic blood pressure lowering may be dose-dependent,

doses of metamizole above 1 g should be used only if there is a definite indication. DEVALJIN injection solution must not be mixed with other drugs in the same syringe.

Additional information on special populations:
Renal / Hepatic impairment:
In patients with renal or hepatic impairment, high doses should be avoided as the elimination rate of metamizole is reduced. However, the dose does not need to be reduced for short-term treatment. There is insufficient experience with long-term treatment in patients with renal or hepatic impairment.

Paediatric population:
Unless medically necessary, DEVALJIN should not be administered to infants under 3 months of age or weighing less than 5 kg. In children under one year of age, DEVALJIN should only be administered intramuscularly.

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

In patients with lower or higher body weight, the dose is reduced or increased as appropriate.

The following dosing schedule may serve as a guide.

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 ages (9-15 kg)	0.2-0.5 ml	0.2-0.5 ml	1.0 g
4 - 6 ages (16-23 kg)	0.3-0.8 ml	0.3-0.8 ml	1.6 g
7 - 9 ages (24-30 kg)	0.4-1.0 ml	0.4-1.0 ml	2.0 g
10 - 12 ages (31-45 kg)	0.5-1.5 ml	0.5-1.5 ml	3.0 g
13 - 14 ages (46-53 kg)	0.8-1.8 ml	0.8-1.8 ml	3.6 g

Geriatric population:
Possible impairment of renal and hepatic function should be considered in elderly patients and patients with impaired general condition.

4.3. Contraindications
- Allergy to metamizole or other pyrazolones (e.g. phenazone, propifenazone) or pyrazolidines (e.g. phenylbutazone, oxyphenbutazone), e.g. previous agranulocytosis to one of these substances
- Impaired bone marrow function (e.g. as a result of cytostatic therapy) or haematopoietic system disorders
- Patients who develop bronchospasm or other anaphylactoid reactions (e.g. urticaria, rhinitis, angioedema) to analgesics such as salicylates, paracetamol, diclofenac, ibuprofen, indomethacin, naproxen
- Allergy to one of the excipients of DEVALJIN
- Acute intermittent hepatic porphyria (risk of induction of porphyria attacks)
- Congenital glucose-6-phosphate dehydrogenase deficiency (risk of haemolysis)
- Babies under 3 months of age or weighing less than 5 kg

In infants aged 3 to 11 months, DEVALJIN should not be administered intravenously.

DEVALJIN should not be administered parenterally in patients with unstable haemodynamics and/or hypotension.

Pregnancy and breast-feeding (see section 4.6)

4.4. Special warnings and precautions for use

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

All patients should be warned that they should stop taking the drug immediately and consult their doctor if any of the following signs or symptoms, possibly associated with neutropenia, occur: fever, chills, sore throat, ulceration of the oral cavity. In case of neutropaenia (<1,500 neutrophils/mm^3), treatment should be discontinued immediately and the complete blood count should be checked immediately and monitored until it returns to normal values.

Pancytopenia: If pancytopenia occurs, treatment should be discontinued immediately and follow-up with complete blood count should be performed until blood values return to normal.

All patients should be warned to seek medical advice immediately if signs and symptoms indicative of blood dyscrasia (e.g. general malaise, infection, persistent fever, bruising, bleeding, pallor) occur during metamizole use.

Anaphylactic shock: This type of reaction occurs mainly in susceptible 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 signs or symptoms of SJS or TEN (progressively worsening skin rashes, usually accompanied by fluid-filled blisters or mucous membrane lesions) develop, metamizole treatment should be discontinued immediately and should never be reintroduced. Patients should be informed about the signs and symptoms and should be closely monitored in terms of 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 of anaphylactic/anaphylactoid reactions.

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

- Patients with bronchial asthma, especially those with concurrent rhinosinusitis polyposis
- Patients with chronic urticaria
- Patients with alcohol intolerance, i.e. patients who react to even small amounts of certain alcoholic beverages with symptoms such as runny nose, lacrimation and marked facial flushing. Alcohol intolerance may be indicative of previously undiagnosed analgesic asthma syndrome.

- Patients with intolerance to dyes (e.g. tartrazine) or preservatives (e.g. benzoates)
- Patients should be carefully questioned before administration of DEVALJIN. In patients found to be at special risk for anaphylactoid reactions, DEVALJIN should be administered after careful consideration of the possible risks and expected benefit. If DEVALJIN is to be used under these conditions, strict medical supervision is required and the necessary conditions for emergency treatment should be in place.

If anaphylactic shock is observed, the following measures should be taken. At the first signs such as sweating, nausea, cyanosis, injection should be stopped immediately. In addition to other usual precautions, the patient is placed head down and the airway is kept open.

Emergency drug therapy:
adrenaline (epinephrine) by i.v. route: For this purpose, 1 ml of a commercially available 1/1000 solution of epinephrine is diluted to 10 ml and 1 ml of this (0.1 mg epinephrine) is injected slowly while monitoring the pulse rate and blood pressure (beware of heart rhythm disturbances!). Epinephrine injections can be repeated if necessary.

Glucocorticoids, e.g. 250-1000 mg methylprednisolone, are then administered i.v. These doses are recommended for an adult of normal weight. In children, the dose should be reduced in relation to body weight. These doses can be repeated if necessary.

Subsequently, volume substitution is performed i.v. with solutions such as plasma expander Human Albumin, complete electrolyte solution.

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 after parenteral administration. Caution should also be exercised in the following situations in order to prevent such severe hypotensive reactions:

- Intravenous injection should be administered slowly.
- Caution should be exercised in patients with impaired haemodynamics with pre-existing hypotension, volume depletion and dehydration, in patients with circulatory instability or circulatory failure at baseline; and
- in patients with high fever.

In such patients, the indication for metamizole should be determined with particular care; if DEVALJIN is to be administered under these conditions, strict medical supervision is required. Preventive measures (stabilisation of haemodynamics) may be necessary to reduce the risk of hypotensive reactions. For patients with hypotension or unstable circulation, see “section 4.3 Contraindications”.

Metamizole should be used only under close haemodynamic monitoring in patients in whom lowering of blood pressure should be avoided, such as patients with severe coronary heart disease or stenosis of the blood vessels supplying the brain.

It is recommended to avoid high doses of metamizole in patients with renal or hepatic impairment, as the rate of metamizole elimination is reduced in these patients.

To ensure that the injection can be stopped at the first sign of an anaphylactic/anaphylactoid reaction (see section 4.8) and to minimise the risk of isolated hypotensive reactions, intravenous injection should be administered very slowly (no more than 1 ml per minute).

DEVALJIN contains 3 mmol (69.3 mg) sodium in each dose. This has to be taken into consideration for patients on a controlled sodium diet.

4.5. Interaction with other medicinal products and other forms of interaction
May reduce cyclosporine levels when used in combination with cyclosporine. Therefore, regular check-ups are necessary.

Severe hypothermia may occur when DEVALJIN is used with chlorpromazine.

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

The addition of metamizole to methotrexate may increase the haematotoxicity of methotrexate, especially in elderly patients. This combination should therefore be avoided.

DEVALJIN is soluble in 5% glucose, 0.9% NaCl or ringer's 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.

4.6. Pregnancy and lactation
General advice
Pregnancy category: C

Women with childbearing potential / Birth control (Contraception)
Women of child-bearing potential should use effective contraceptive measures during treatment.

Pregnancy
Metamizole crosses the placenta. There is no evidence that the drug is harmful to the foetus: Metamizole did not show teratogenic effects in rats and rabbits and fetotoxicity was observed only at high doses that were also maternally toxic. However, clinical data on the use of DEVALJIN during pregnancy are insufficient.

Therefore, it is not recommended to use DEVALJIN in the first trimester of pregnancy. In the following three months, it is only used after the potential benefits and risks have been carefully weighed by a doctor.

However, DEVALJIN should not be used in the last trimester of pregnancy. Because, although metamizole is only a weak prostaglandin synthesis inhibitor, the possibility of perinatal complications due to premature closure of the ductus arteriosus and impairment of both maternal and neonatal platelet aggregability cannot be ruled out.

Breast-feeding
Metabolites of metamizole are excreted in breast milk. Breastfeeding should be avoided during and for 48 hours after administration of DEVALJIN.

Fertility
Studies in rats and rabbits have not shown teratogenic potential.

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 recognised that, at least at high doses, concentration and reaction ability may be impaired and that there may be a risk in situations where this ability is of particular importance (e.g. driving or operating machinery) (especially if alcohol is involved).

4.8. Undesirable effects
Adverse drug reactions are indicated according to the following frequency:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Blood and lymphatic system disorders
Rare: Pancytopenia, aplastic anaemia, agranulocytosis and leucopenia, which can result in death
Very rare: Thrombocytopaenia
These reactions are considered to be of immunological origin. These can still occur even if DEVALJIN has been used many times before without any complications.

Typical manifestations of agranulocytosis are inflammatory mucosal lesions (e.g. oropharyngeal, anorectal, genital), sore throat, fever (sometimes even unexpectedly persistent or recurrent fever). However, typical signs of agranulocytosis may be minimal in patients treated with antibiotics.

The erythrocyte sedimentation rate is very increased and the lymph nodes are typically mildly enlarged or not enlarged.

Typical signs of thrombocytopenia are increased bleeding tendency and petechiae on the skin and mucous membranes.

Immune system disorders
Anaphylactic/anaphylactoid reactions

Rare: Metamizole may 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 DEVALJIN has been used many times before without

causing any complaints.

Such reactions may occur immediately or hours after metamizole administration. However, the usual situation here is that the reaction occurs within the first hour after application.

Moderate anaphylactic/anaphylactoid reactions typically present as cutaneous and mucosal symptoms (such as itching, burning, flushing, urticaria, wheals), dyspnoea and more frequently gastrointestinal complaints.

Mild reactions may progress over time to severe forms with generalised urticaria, severe angioedema (even involving the larynx), severe bronchospasm, cardiac arrhythmias, drop in blood pressure (sometimes preceded by an increase in blood pressure) and circulatory shock.

In patients with analgesic asthma syndrome, these intolerance reactions typically manifest as asthma attacks.

Vascular disorders
Unknown: Isolated hypotensive reactions
Occasionally, transient isolated hypotensive reactions may occur during or after administration (probably of pharmacological origin and without 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 hypotensive reactions.

Skin and subcutaneous disorders
Rare: Maculopapulous rash.
Very rare: Stevens-Johnson syndrome or Lyell syndrome, circulatory shock.
Frequency unknown: In addition to the cutaneous and mucosal anaphylactic/anaphylactoid manifestations mentioned above, occasional fixed drug eruptions (see section 4.4).

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

Red colouration of the urine is sometimes observed; this may be due to a metabolite (rubazonic acid) present in low concentration.

General disorders and administration site conditions
Pain and local reactions may occur at the injection site. Phlebitis may sometimes be added to the picture.

4.9. Overdose
Symptoms:
Nausea, vomiting, abdominal pain, renal dysfunction/acute renal failure (e.g. due to interstitial nephritis) and, more rarely, central nervous system symptoms (dizziness, somnolence, coma, convulsions), decreased blood pressure (which can sometimes develop into shock) and cardiac arrhythmias (tachycardia) have been reported following acute overdose. After very high doses, urine may turn red in colour as a result of excretion of a harmless metabolite (rubazonic acid).

Treatment:
Metamizole has no known specific antidote. If the drug has just been taken, measures for primary detoxification (e.g. gastric lavage) or to reduce absorption (e.g. activated charcoal) may be taken to limit further systemic absorption of active substances. The main metabolite of the drug (4-N-methylaminoantipyrine) can be eliminated by haemodialysis, haemofiltration, haemoperfusion or plasma filtration.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Pyrazolones
ATC code: N02BB02

Metamizole has analgesic, antipyretic and antispasmodic effects. Metamizole most likely has a combined central and peripheral mode of action. Central mechanisms of action at the level of afferent fibres, vertebral marrow and periquaductal grey matter may contribute to the analgesic effect of metamizole.

The mechanism of action is not entirely clear. Some data suggest that metamizole and its main metabolite (4-N-methylaminoantipyrine) may have a combined central and peripheral mode of action.

5.2. Pharmacokinetic properties

The pharmacokinetics of metamizole and its metabolites have not been fully investigated. But the following information can be given:

Absorption: After oral administration, metamizole is completely hydrolysed to its active metabolite 4-N-methylaminoantipyrine (MAA). The absolute bioavailability of MAA is approximately 90% and is slightly higher after oral administration than after intravenous administration. Since metamizole is taken with food, the pharmacokinetics of MAA are not noticeably altered.

Biotransformation: The clinical effect is mainly provided by MAA and to some extent by 4-aminoantipyrine (AA). The AUC of AA is approximately 25% of the AUC of MAA. Metabolites such as 4-N-acetylaminoantipyrine (AAA) and 4-N-formylaminoantipyrine (FAA) appear to have no clinical effects. A non-linear pharmacokinetics is observed for all metabolites. Further studies are needed to make a judgement about the clinical significance of this finding. In short-term treatment, the accumulation of metabolites has little clinical significance.

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

Elimination: Approximately 96% of the radiolabelled intravenous dose is excreted in urine and approximately 6% in faeces. After a single oral dose, 85% of the metabolites were excreted in the urine, of which 3±1% was MAA, 6±3% was AA, 26±8% was AAA and 23±4% was FAA. After a single 1 g oral dose of metamizole, renal clearance was 5 ml±2 ml/min for MAA, 38 ml±13 ml/min for AA, 61 ml±8 ml/min for AAA, and 49 ml±5 ml/min for FAA. Plasma half-lives after the same dose were 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/non-linearity: A non-linear pharmacokinetics is observed for all metabolites. Further studies are needed to make a judgement about the clinical significance of this finding.

Characteristics in patients
Geriatric population:
Drug exposure (AUC) increases 2-3-fold in the elderly.

Hepatic insufficieny:
In patients with liver cirrhosis, the half-life of MAA and FAA increased 3-fold (10 hours) after single oral administration, but the increase in AA and AAA was not as marked.

Renal insufficiency:
Patients with impaired renal function have not been studied with sufficient intensity. Available data suggest 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 are: orally approximately 4000 mg/kg body weight; intravenously approximately 2300 mg metamizole/kg body weight or 400 mg MAA/kg body weight.

Symptoms of intoxication were tachypnoea, sedation and premortal convulsions.

Chronic toxicity:
Administration of metamizole at doses of 150 mg/kg body weight per day in rats and 50 mg/kg body weight per day in dogs for 4 weeks was tolerated.

Subchronic and chronic toxicity studies were carried out in different animal species. Rats were administered metamizole at a daily dose of 100-900 mg/kg body weight for 6 months. At the highest dose (900 mg/kg), reticulocytes and Heinz bodies increased after 13th week.

Dogs were administered metamizole at daily doses of 30-600 mg/kg body weight for 6 months. Dose-related haemolytic anaemia and impairment of renal and hepatic functions were observed from doses of 300 mg/kg per day.

Higher doses caused changes in serum chemistry and haemosiderosis of the liver and spleen in both sexes, as well as signs of bone marrow toxicity and anaemia.

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

Carcinogenicity:
No evidence of carcinogenic potential was found in long-term studies in rats. In two of three long-term studies, an increase in liver cell adenomas was reported at high doses.

Mutagenicity:
Both positive and negative results have been described in the literature. However, *in-vitro* and

in-vivo studies with the Hoechst-graded material have not shown any evidence of mutagenic potential.

Reproductive toxicity:
No teratogenic potential was demonstrated in embryotoxicity studies in rats and rabbits.
In rabbits, lethal effects have been reported at a dose of 100 mg/kg/day without maternal toxicity. Fatal embryotoxic effects in rats occurred in the dose range in which maternal toxicity was observed. In rats, doses above 100 mg/kg/day resulted in prolonged gestation and impaired labour process, as well as increased mortality in offspring.
Fertility tests have shown a slight decrease in the pregnancy rate of the fertile generation at doses above 250 mg/kg/day. The fertility of the F1 generation was not affected.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Sodium metabisulfite
Water for injection

6.2. Incompatibilities
Not applicable.

6.3. Shelf life
60 months.

6.4. Special precautions for storage
It should be stored at room temperature below 25°C and in its packaging.

6.5. Nature and contents of container
2 ml amber-coloured ampoules with ring made of type I glass.
Each cardboard box contains 5 or 10 2 ml ampoules.
* Not all pack sizes may be available.

6.6. Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER
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