

## **SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

<Invented Name> 500 mg tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg of metamizole sodium

Excipient(s) with known effect: Each tablet contains approximately 32.78 mg sodium, (equivalent to 1.423 mmol sodium).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablet.

White to off white, round, biconvex tablets. Plain on one side and breakline on the other side.

Diameter: 12 mm. Thickness: 7 mm.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

<Invented Name> 500 mg tablets are indicated in adults and children aged 10 years and older in

- acute severe pain after injuries or surgery
- colic
- tumour pain
- other acute or chronic severe pain, where other therapeutic measures are not indicated
- high fever that does not respond to other measures

### 4.2 Posology and method of administration

#### Posology

Dosage is determined by the intensity of the pain or fever and individual sensitivity of response to <Invented Name>.

It is essential to choose the lowest dose that controls pain and fever.

#### *Adults*

Adults and adolescents from 15 years of age on (> 53 kg) can take up to 1000 mg per individual dose. Where the effect is inadequate, the respective dose can be administered up to 4 times daily, depending on the maximum daily dose.

The following dosage tables set out the recommended individual doses and maximum daily doses.

Dosage table for <Invented Name> 500 mg tablets:

Age (body weight)	Individual dose	Maximum daily dose
10-14 years (32-53 kg)	1 film-coated tablet <Invented Name> (corresponding to 500 mg metamizole sodium monohydrate	up to 4 film-coated tablets <Invented Name> (corresponding to up to

		2.000 mg metamizole sodium monohydrate
Adults and adolescents aged 15 years and over (> 53 kg)	1 to 2 film-coated tablets <Invented Name> (corresponding to 500-1.000 mg metamizole sodium monohydrate)	up to 8 film-coated tablets <Invented Name> (corresponding to 4.000 mg metamizole sodium monohydrate)

#### Duration of use

The duration of use is determined by the nature and severity of the condition. In the case of longer-term therapy with <Invented Name>, regular blood counts including a differential blood count are required.

#### *Older People*

In the case of elderly patients, the dose should be reduced, as excretion of the metabolic products of <Invented Name> may be delayed.

#### *Patients with reduced general health and impaired creatinine clearance*

In patients with reduced general health and impaired creatinine clearance, the dose should be reduced, as excretion of the metabolic products of <Invented Name> may be delayed.

#### *Impaired renal or hepatic function*

As the elimination rate is reduced when renal or hepatic function is impaired, multiple high doses should be avoided. No dose reduction is needed when used for only a short time. There is no experience of long-term use.

#### *Paediatric population*

In the case of fever, a dose of 10 mg metamizole per kilogram body weight is generally sufficient for children.

A clear effect can be expected 30 to 60 minutes after oral administration.

In the case of children and adolescents up to 14 years old, 8 to 16 mg metamizole per kilogram body weight is to be administered as an individual dose.

<Invented Name> should not be used in children aged under 10 years old (see section 4.3).

#### Method of administration

Oral use.

The tablets are taken whole and with sufficient fluid (e.g. a glass of water).

### **4.3 Contraindications**

<Invented Name> must not be used:

- in the case of hypersensitivity to metamizole or other pyrazolones or pyrazolidines (this also includes patients who have, for example, developed agranulocytosis after the use of these substances) or to any of the excipients of <Invented Name>
- in patients with known analgesic asthma syndrome or known analgesic intolerance of the urticaria/angio-oedema type, i.e. patients who react with bronchospasm or other anaphylactoid types of reaction (e.g. urticaria, rhinitis, angioedema) to salicylates, paracetamol or other non-narcotic analgesics, such as diclofenac, ibuprofen, indomethacin or naproxen
- in the case of disturbances of bone marrow function (e.g. after cytostatic therapy) or diseases of the haematopoietic system
- in the case of genetically related glucose-6-phosphate dehydrogenase deficiency (danger of haemolysis)

- in the case of acute intermittent hepatic porphyria (risk of inducing an attack of porphyria)
- in the third trimester of pregnancy (see section 4.6)
- during the lactation period
- in children under 10 years old

#### **4.4 Special warnings and precautions for use**

<Invented Name> contains the pyrazolone derivative metamizole and possesses the rare, but life-threatening risks of shock and agranulocytosis (see section 4.8).

Patients who exhibit anaphylactoid reactions to <Invented Name> are also at particular risk of reacting in the same way to other non-narcotic analgesics.

Patients who exhibit an anaphylactic or other immunologically mediated reaction to <Invented Name> (e.g. agranulocytosis) are also at particular risk of reacting in the same way to other pyrazolones or pyrazolidines.

##### Agranulocytosis

If signs of agranulocytosis or thrombocytopenia occur, (see section 4.8), <Invented Name> must be discontinued immediately and the blood count (including differential blood count) tested. Discontinuation of therapy must not be postponed until the laboratory test results are available.

##### Pancytopenia

If signs of pancytopenia occur treatment must be discontinued immediately and complete blood count must be checked until normalization (see section 4.8). All patients should be instructed to consult their doctor immediately if signs and symptoms occur during treatment which may indicate blood dyscrasia (e.g. bad general feeling, infections, persisting fever, bruising, bleeding, paleness).

##### Anaphylactic/anaphylactoid reactions

The danger of potentially severe anaphylactoid reactions to <Invented Name> is markedly higher for patients with:

- analgesic asthma syndrome or analgesic intolerance of the urticaria/angio-oedema type (see section 4.3),
- bronchial asthma, in particular with co-existing rhinosinusitis and nasal polyps
- chronic urticaria,
- intolerance to dyes (e.g. tartrazine) or preservatives (e.g. benzoates),
- alcohol intolerance. Such patients react to only small quantities of alcoholic drinks with symptoms such as sneezing, lacrimation, and severe facial flushing. This alcohol intolerance may indicate a previously undiagnosed analgesic asthma syndrome (see section 4.3).

An anaphylactic shock may predominantly occur in sensitive patients. Particular care should be taken for application in patients with asthma or atopy.

##### Severe skin reactions

Life-threatening skin-reactions as Stevens-Johnson-Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been observed upon administration of Metamizole. If symptoms or signs of SJS or TEN become apparent (such as progressive rash frequently associated with blisters or lesion of the mucosa), treatment must be immediately discontinued and must never be restarted.

Patients should be informed on these signs and symptoms and should be closely monitored for skin reactions, especially during the first weeks of treatment.

### Isolated hypotensive reactions

<Invented Name> may induce hypotensive reactions (see section 4.8). These reactions may be dose-dependent. This is more likely with parenteral than enteral administration. The risk of such reactions is also increased in the case of:

- patients with, for example, pre-existing hypotension, volume deficiency or dehydration, unstable circulation or incipient circulatory failure (such as patients with myocardial infarction or multiple trauma),
- patients with high fever.

Therefore in these patients the indication must be carefully established and close monitoring undertaken. Preventive measures (e.g. circulatory stabilisation) may be needed to reduce the risk of hypotensive reactions.

In patients in whom a fall in blood pressure must be avoided under all circumstances, such as in severe coronary heart disease or relevant stenosis of vessels supplying the brain, <Invented Name> should be used only if the haemodynamic parameters are monitored closely.

In patients with disturbances of renal and hepatic function, <Invented Name> should be used only after careful assessment of the risks and benefits and appropriate precautions (see section 4.2).

Patients should be questioned accordingly prior to the administration of <Invented Name>. In patients at increased risk of anaphylactoid reactions, <Invented Name> should be used only after carefully weighing up potential risks against the expected benefit. If <Invented Name> is administered in such cases, the patient should be closely monitored medically and emergency facilities should be available.

This medicinal product contains 1.423 mmol sodium per tablet. To be taken into consideration by patients on a controlled sodium diet.

## **4.5 Interaction with other medicinal products and other forms of interaction**

Metamizole can cause a decrease in serum cyclosporin levels. These levels must therefore be monitored if <Invented Name> is used at the same time.

With combined use of <Invented Name> and chlorpromazine, severe hypothermia may occur.

Application of metamizole in addition to methotrexate may increase hemotoxicity of methotrexate, especially in elderly patients. Thus, this combination should be avoided.

Metamizole may diminish the anti-platelet activity of low-dose acetylsalicylic acid during concomitant use. Metamizole therefore should be used with caution in patients taking low-dose acetylsalicylic acid for cardioprotection.

Metamizole may lower Bupropion blood-levels. Caution has therefore to be advised when Metamizole and Bupropion are used concomitantly.

The class of substances of pyrazolones are known potentially to interact with oral anticoagulants, captopril, lithium and triamterene and can alter the efficacy of antihypertensive agents and diuretics. It is not known to what extent metamizole also leads to such interactions.

## **4.6 Fertility, pregnancy and lactation**

### *Pregnancy*

There are no adequate data from the use of <Invented Name> in pregnant women. Metamizole crosses the placental barrier. In studies in animals metamizole exhibited no teratogenic effects (see section 5.3). As no adequate experience is available for humans, <Invented Name> should not be taken during the 1<sup>st</sup> trimester and during the 2<sup>nd</sup> trimester of pregnancy only after a strict medical benefit/risk assessment.

Although metamizole is only a weak prostaglandin synthesis inhibitor, the possibility of premature closure of the ductus arteriosus (ductus Botalli), as well as perinatal complications due to a reduction in platelet aggregation in the child and mother, cannot be excluded. <Invented Name> is therefore contra-indicated during the last trimester of pregnancy (see section 4.3).

#### *Breast-feeding*

The metabolites of metamizole are excreted into breast milk, and breast-feeding must therefore be avoided during intake/administration and for at least 48 hours after the last intake/administration of (see section 4.3) <Invented Name>.

#### **4.7 Effects on ability to drive and use machines**

Within the recommended dosage range there is no known impairment of the ability to concentrate and react. As a precaution, however, at least at higher dosages, the possibility of impairment should be considered and patients should not use machines, drive vehicles or engage in other hazardous activities. This applies particularly in conjunction with alcohol.

#### **4.8 Undesirable effects**

The following categories are used in assessing the frequency of side effects:

<b><i>very common</i></b>	≥ 1/10
<b><i>common</i></b>	≥ 1/100 to < 1/10
<b><i>uncommon</i></b>	≥ 1/1000 to < 1/100
<b><i>rare</i></b>	≥ 1/10,000 to < 1/1000
<b><i>very rare</i></b>	<1/10,000
<b><i>not known</i></b>	cannot be estimated from the available data

The main undesirable effects of metamizole sodium are derived from hypersensitivity reactions. The most significant are shock and agranulocytosis. These reactions occur rarely or very rarely, but are life-threatening and may also occur if metamizole sodium was previously given without complications.

#### *Blood and lymphatic system disorders*

*Rare:* leukopenia

*Very rare:* agranulocytosis including cases with fatal outcome or thrombocytopenia.

*Not known:* Aplastic anemia, pancytopenia, including cases with fatal outcome.

These reactions can also occur even if previous administration of metamizole sodium was without complications.

There is some evidence that the risk of agranulocytosis increases if metamizole sodium is administered for longer than one week. This reaction does not depend on dosage and may occur any time during treatment. It is characterised by high fever, chills, sore throat, swallowing difficulties as well as inflammation in the area of the mouth, nose, throat and genital or anal region). In patients receiving antibiotics, these signs may, however, be minimal. There is little or no swelling of the lymph nodes or spleen. The erythrocyte sedimentation rate (ESR) is markedly accelerated, the granulocytes are reduced considerably or completely absent. In general, but not always haemoglobin, erythrocyte and platelet values are normal (see section 4.4).

Immediate discontinuation is essential for recovery. It is therefore strongly recommended to discontinue <Invented Name> immediately, without waiting for the results of laboratory-diagnostic tests, if an unexpected deterioration of the general condition occurs, fever persists or newly occurs or painful mucosal changes occur (mainly in the mouth, nose and throat region).

If pancytopenia occurs, treatment must be stopped immediately and complete blood count must be monitored until normalization (see section 4.4).

#### *Immune system disorders*

*Rare:* anaphylactoid or anaphylactic reactions\*.

*Very rare:* analgesics-induced asthma-syndrome.

In patients with analgesics asthma syndrome intolerance typically take the form of asthma attacks.

*Not known:* anaphylactic shock\*.

\* These reactions mainly occur during parenteral application and may be severe and life-threatening, in some cases even fatal. They can also occur if metamizole has been previously tolerated without complications.

Such reactions to medicinal products may occur during the injection, immediately after administration or may also develop hours afterwards; in the majority of cases, however, they occur during the first hour post-administration.

Milder reactions typically take the form of skin and mucosal reactions (e.g. pruritus, a burning sensation, redness, urticaria, swelling), dyspnoea and, more rarely, gastrointestinal complaints (e.g. nausea, dyspepsia, vomiting). Such mild reactions may become severe with generalised urticaria, severe angioedema (including laryngeal oedema), severe bronchospasm, cardiac arrhythmias, a fall in blood pressure (sometimes also with a preceding rise in blood pressure) and circulatory shock. In patients with analgesic asthma syndrome, intolerance reactions typically take the form of asthma attacks.

At the first signs of shock, such as a cold sweat, dizziness, light-headedness, skin discoloration, a sensation of discomfort around the heart, the necessary emergency measures should be initiated.

Metamizole therefore has to be immediately discontinued if skin reactions occur.

#### *Cardiac disorders*

*Not known:* Kounis syndrome

#### *Vascular disorders*

*Uncommon:* hypotensive reactions during or after administration, which may be pharmacological in origin and not accompanied by other signs of anaphylactoid or anaphylactic reaction. Such reactions may lead to a severe fall in blood pressure. Rapid intravenous injection increases the risk of such a hypotensive reaction.

Depending from dose, a critical drop in blood pressure may also occur in the case of hyperpyrexia without further signs of hypersensitivity.

#### *Skin and subcutaneous tissue disorders*

*Uncommon:* fixed drug exanthema

*Rare:* rash (maculo-papular exanthema)

*Very rare:* Stevens-Johnson syndrome or toxic epidermal necrolysis (discontinue treatment, see section 4.4).

#### *Renal and urinary disorders*

*Very rare:* acute deterioration of renal function, which may very rarely progress to proteinuria, oliguria or anuria or acute renal failure, acute interstitial nephritis.

#### *General disorders and administration site conditions*

Red discoloration of the urine has been reported. This can be attributed to the harmless metamizole metabolite rubazonic acid which exists in low concentration.

## 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. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system listed in Appendix V**.

### **4.9 Overdose**

#### *Symptoms:*

Nausea, vomiting, abdominal pain, renal impairment/acute renal failure (e.g. in the form of interstitial nephritis) and – more rarely – central nervous symptoms (dizziness, somnolence, coma, convulsions) and a fall in blood pressure that can progress to shock and tachycardia have been observed in association with acute overdoses.

After very high doses, excretion of rubazonic acid may cause red discolouration of the urine.

#### *Therapeutic measures:*

No specific antidote is known for metamizole. If metamizole has been ingested recently, an attempt may be made to limit absorption in the body by measures of primary detoxification (e.g. gastric lavage) or by absorption-reducing measures (e.g. activated charcoal). The main metabolite (4-N-methylaminoantipyrine) can be eliminated by haemodialysis, haemofiltration, haemoperfusion or plasma filtration.

The treatment of intoxication, as well as the prevention of severe complications, may require general and special intensive medical monitoring and treatment.

#### *Immediate measures if severe hypersensitivity reactions (shock) occur:*

Discontinue if first signs of hypersensitivity (e.g. cutaneous reactions such as urticaria and flushing, restlessness, headache, sweating attacks, nausea) occur. a venous access. Apart from common emergency measures such as Trendelenburg position, maintenance of patent airways and oxygen application the administration of sympathomimetics, volume expanders or glucocorticoids may be necessary.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pyrazolone derivative

Pharmacotherapeutic group: Other analgesics and antipyretics; Pyrazolones

ATC code: N02B B02

Metamizole is a pyrazolone derivative and has analgesic, antipyretic and spasmolytic properties. The mechanism of action is not fully elucidated. Some study results show that metamizole and the main metabolite (4-N-methylaminoantipyrine) possibly have both a central and a peripheral mechanism of action.

### **5.2 Pharmacokinetic properties**

Metamizole is completely hydrolysed to the pharmacologically active 4-N-methylaminoantipyrine (MAA) after oral administration. The bioavailability of MAA is about 90% and is somewhat higher after oral administration than after parenteral administration. The concomitant ingestion of food has no relevant effect on metamizole kinetics.

The clinical efficacy is due predominantly to MAA, but also to a certain extent to the metabolite 4-aminoantipyrine (AA). The AUC values for AA represent about 25% of the AUC values for MAA.

The metabolites 4-N-acetylaminoantipyrine (AAA) and 4-N-formylaminoantipyrine (FAA) are apparently pharmacologically inactive.

It should be noted that all metabolites have non-linear pharmacokinetics. The clinical significance of this phenomenon is not known. In short-term treatment the accumulation of metabolites is insignificant.

Metamizole crosses the placental barrier. The metabolites of metamizole are excreted in the breast milk.

Plasma protein binding is 58% for MAA, 48% for AA, 18% for FAA and 14% for AAA.

After intravenous administration the plasma half-life of metamizole is about 14 minutes. About 96% of a radiolabelled dose is recovered in the urine and about 6% in the faeces after intravenous administration. After a single oral dose 85% of the metabolites eliminated in the urine were identified. Of this, MAA accounted for  $3 \pm 1\%$ , AA for  $6 \pm 3\%$ , AAA for  $26 \pm 8\%$  and FAA for  $23 \pm 4\%$ . Renal clearance after a single oral dose of 1 g metamizole was  $5 \pm 2$  ml/min for MAA,  $38 \pm 13$  ml/min for AA,  $61 \pm 8$  ml/min for AAA and  $49 \pm 5$  ml/min for FAA. The associated plasma half-lives were  $2.7 \pm 0.5$  hours for MAA,  $3.7 \pm 1.3$  hours for AA,  $9.5 \pm 1.5$  hours for AAA and  $11.2 \pm 1.5$  hours for FAA.

In the treatment of elderly patients the AUC is increased 2- to 3-fold. After a single oral administration the half-life of MAA and FAA in patients with hepatic cirrhosis increased about 3-fold, whereas the half-life of AA and AAA did not increase to the same extent. High doses should be avoided in these patients.

The available data for patients with impaired renal function show a reduced elimination rate for some metabolites (AAA and FAA). High doses should therefore be avoided in these patients.

#### Bioavailability

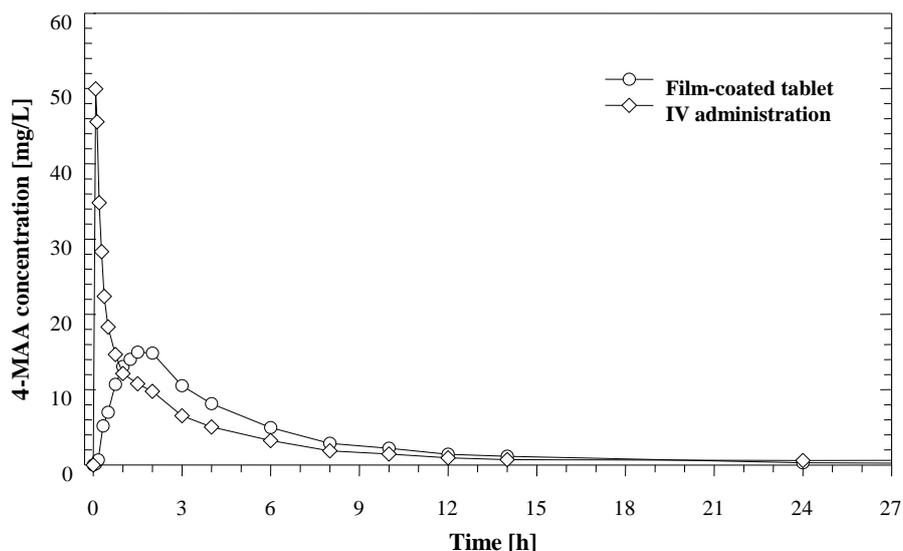
A bioavailability study of the originator's film-coated tablet of metamizole conducted in 1987 in 12 volunteers in comparison with the reference product (IV administration over 2 minutes) revealed for 4-MAA:

	Film-coated tablet (1 g)	IV administration (1 g)
Peak plasma concentration ( $C_{max}$ ) [mg/L]	$17.3 \pm 7.54$	$56.5 \pm 12.2$
Time to peak plasma concentration ( $t_{max}$ ) [h]	$1.42 \pm 0.54$	End of injection
Area under the concentration-time curve (AUC) [mg x h/L]	$80.9 \pm 34.1$	$71.2 \pm 13.7$

(Values given as mean and standard deviation)

The absolute bioavailability of the originator's film-coated tablet measured in terms of the AUC of the 4-MAA plasma concentrations is 93%.

Mean plasma level profiles compared to a reference product on a concentration-time plot:



### 5.3 Preclinical safety data

Subchronic and chronic toxicity studies exist in various species. Rats received 100 to 900 mg metamizole per kg body weight orally for 6 months. At the highest dose (900 mg per kg BW) an increase in reticulocytes and Heinz bodies was observed after 13 weeks.

Dogs received metamizole at doses of 30 to 600 mg per kg body weight for 6 months. Haemolytic anaemia and functional renal and hepatic changes were observed dose-dependently at doses of 300 mg per kg body weight and above.

There are contradictory results for metamizole from in vitro and in vivo studies in the same test systems.

There was no evidence of a tumorigenic potential in long-term studies in rats. In two out of three long-term studies in the mouse increased numbers of hepatic adenomas were observed at high doses.

Embryotoxicity studies in rats and rabbits showed no evidence of teratogenic effects.

Embryolethal effects have been observed in rabbits at a not yet maternotoxic daily dose of 100 mg per kg body weight. Embryolethal effects occurred in rats at doses in the maternotoxic range. Daily doses of more than 100 mg per kg body weight in rats resulted in a prolongation of gestation and impairment of the birth process with increased mortality in mother animals and offspring.

Fertility tests showed a slightly reduced gestation rate in the parental generation at a dose above 250 mg per kg body weight and per day. The fertility of the F1 generation was not affected.

The metabolites of metamizole are excreted in the breast milk. There is no experience concerning the effects in infants.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Mannitol  
 Hydroxypropylcellulose  
 Crospovidone (Type A)  
 Croscarmellose sodium  
 Magnesium stearate

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

2 years

## **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

## **6.5 Nature and contents of container**

PVC/PVDC –Aluminium blisters

Pack sizes: 10, 20, 30 and 50 tablets. Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal**

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7. MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

## **8. MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: {DD month YYYY}

Date of latest renewal: {DD month YYYY}

[To be completed nationally]

## **10. DATE OF REVISION OF THE TEXT**

{MM/YYYY}

[To be completed nationally]