Summary of Product Characteristics

Optalgin® Teva 1 g/2 ml
Solution for I.V. or I.M. Injection

1. NAME OF THE MEDICINAL PRODUCT

Optalgin® Teva 1 g/2 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 500 mg dipyrone (metamizole sodium).

Each ampoule of 2 ml solution for injection contains 1g dipyrone.

Excipient with known effect:
Each ampoule of 2 ml solution for injection contains 65 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

As an Analgesic
Optalgin® Teva 1 g/2 ml solution for injection, by intravenous administration, is indicated for the relief of severe and acute pain when oral treatment is not feasible or suitable, as in post-traumatic or post-surgical pain, biliary or renal colic, and pain associated with malignant diseases.

As an Antipyretic
Optalgin® Teva 1 g/2 ml solution for injection, by intramuscular administration, is indicated to lower temperature in life-threatening situations, when this cannot be achieved by other means.
Hyperthermic patients in critical condition may also be treated in a non-hospital environment, under close medical supervision.

4.2 Posology and method of administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Adults and Adolescents Over 14 Years of Age

Intravenous Administration as an Analgesic
1 g (2 ml), administered by slow injection, up to 4 times daily.
In severe pain, 2.5 g (5 ml) may be administered twice daily (the maximum daily dosage is 5 g).

Intravenous administration of dipyrone should be carried out slowly over a period of at least 5 minutes, followed by reasonable clinical observation.

Intramuscular administration of dipyrone for relief of pain is not recommended. However, if medical circumstances require such administration, all due precautions should be exercised to permit reasonable clinical observation.

Intramuscular Administration as an Antipyretic
2.5 g (5 ml), to be repeated only if deemed necessary.

Infants and Children
Use of dipyrone is contraindicated in infants under 3 months of age or 5 kg/body weight.

In infants 3-12 months, Optalgin® Teva 1 g/2 ml solution for injection must be administered by the intramuscular route only. In older children, the injection may be administered by either the intramuscular or intravenous routes.

Dosage guidelines for the administration of Optalgin® Teva 1 g/2 ml solution for injection as an analgesic and/or antipyretic, in infants over 3 months of age and in children, are presented in the table below.

Optalgin® Teva 1 g/2 ml solution for injection - Dosage Guidelines in Infants and Children

Age	Smallest Single Dosage	Maximum Daily Dosage
3-5 months	0.1 ml I.M. only	4 x 0.2 ml
6-11 months	0.1 ml I.M. only	4 x 0.3 ml
1-2 years	0.2 ml I.M./I.V.	4 x 0.4 ml
3-4 years	0.2 ml I.M./I.V.	4 x 0.6 ml
5-7 years	0.4 ml I.M./I.V.	4 x 0.8 ml
8-11 years	0.5 ml I.M./I.V.	4 x 1.0 ml
12-14 years	0.8 ml I.M./I.V.	4 x 1.6 ml

Special populations

Elderly population, debilitated patients and patients with reduced creatinine clearance

The dose should be reduced in elderly people, in debilitated patients and in those with reduced creatinine clearance, as elimination of the metabolic products of dipyrone may be prolonged.

Hepatic and renal impairment

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 only for a short time. To date, there has been insufficient experience with long-term use of dipyrone in patients with severe hepatic and renal impairment.

Duration of administration
The duration of administration depends on the nature and severity of the disorder.

4.3 Contraindications

- Hypersensitivity to the active substance or to other pyrazolones or pyrazolidines or to any of the excipients listed in section 6.1.
- Agranulocytosis in the medical history induced by dipyrone, other pyrazolones or pyrazolidines.
- Patients with known analgesic asthma syndrome or known urticaria/angio-oedema type intolerance of analgesics, i.e., patients who react with bronchospasm or other anaphylactoid reactions (e.g., urticaria, rhinitis, angio-oedema) to salicylates, paracetamol or other non-narcotic analgesics such as diclofenac, ibuprofen, indomethacin or naproxen.
- Impaired bone marrow function or diseases of the hematopoietic system.
- Acute intermittent hepatic porphyria (risk of triggering a porphyria attack).
- Existing hypotension and unstable circulatory situation.
- Newborn babies and infants under 3 months of age or weighing less than 5 kg, as no scientific data are available on the safety of its use.
- Infants (aged 3 months to 1 year) with regard to intravenous injection.

4.4 Special warnings and precautions for use

Agranulocytosis
Treatment with dipyrone can cause agranulocytosis, which may be fatal (see section 4.8). It may occur even after dipyrone has previously been used without complications.

Dipyrone-induced agranulocytosis is an idiosyncratic adverse reaction. It is not dose-dependent, and may occur at any time during treatment, even shortly after treatment discontinuation.

Patients must be instructed to discontinue their treatment and seek immediate medical attention in case any symptoms suggestive of agranulocytosis appear (e.g. fever, chills, sore throat and painful mucosal changes, especially in the mouth, nose and throat or in the genital or anal region).

If dipyrone is taken for fever, some symptoms of emerging agranulocytosis may go unnoticed. Similarly, symptoms may also be masked in patients receiving antibiotic therapy.

If signs and symptoms suggestive of agranulocytosis occur, a complete blood cell count (including differential blood count) should be performed immediately, and treatment must be stopped while waiting for the results. If confirmed, treatment must not be reintroduced (see section 4.3).

Optalgin® Teva 1 g/2 ml solution for injection is associated with the rare but life-threatening risks of shock and agranulocytosis (see section 4.8).

Patients who display anaphylactoid reactions to dipyrone are at particular risk of reacting in the same way to other non-narcotic analgesics.

Patients who display an anaphylactic or other immunologically mediated reaction (e.g. agranulocytosis) to dipyrone are also at particular risk of reacting in the same way to other pyrazolones and pyrazolidines.

Patients who display an anaphylactic or other immunologically mediated reaction to other pyrazolones, pyrazolidines or other non-narcotic analgesics are also at high risk of having such a reaction to dipyrone (see section 4.3).

Thrombocytopenia
If signs of thrombocytopenia occur, such as an increased bleeding tendency and petechiae on the skin and mucosae (see section 4.8), the use of Optalgin Teva 1g/2ml solution for injection must be stopped immediately and the blood count (including differential count) checked. Do not wait for the results of the laboratory tests before stopping the treatment.

Pancytopenia
If pancytopenia occurs, the treatment must be stopped immediately and the full blood count monitored until it normalises (see section 4.8). All patients should be informed that they should consult the doctor immediately if signs and symptoms indicating blood dyscrasia occur during the treatment (e.g., general malaise, infection, persistent fever, bruising, bleeding, pallor).

Anaphylactic/Anaphylactoid reactions
In choosing the route of administration, it must be borne in mind that parenteral administration of dipyrone is associated with a higher risk of anaphylactic or anaphylactoid reactions.

The risk of potentially serious anaphylactoid reactions to dipyrone is distinctly higher in patients with:
- analgesic asthma syndrome or urticaria/angio-oedema type intolerance of analgesics (see section 4.3).
- bronchial asthma, especially if accompanied by rhinosinusitis and nasal polyps,
- chronic urticaria.
- intolerance of dyes (e.g. tartrazine) and preservatives (e.g. benzoates).
- alcohol intolerance. Such patients react even to small quantities of alcoholic drinks with symptoms such as sneezing, eye watering and pronounced facial reddening. An alcohol intolerance of this kind can be a sign of a previously undiagnosed analgesic asthma syndrome (see section 4.3).

Anaphylactic shock can occur, primarily in sensitive patients. Particular caution is therefore indicated in the case of administration to patients with asthma or atopy.
The patient must be asked about this before the administration of Optalgin Teva 1g/2ml solution for injection. In patients with an increased risk for anaphylactoid reactions, Optalgin Teva 1g/2ml solution for injection may be used only after carefully weighing the possible risks against the expected benefit (see also section 4.3). If Optalgin Teva 1g/2ml solution for injection is administered in such cases, the patient must be closely monitored by a doctor, ensuring emergency equipment is on standby.

Severe skin reactions
Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening, or fatal, have been reported in connection with dipyrone therapy.

The patients are to be informed about the signs and symptoms and monitored closely for skin reactions.

If signs and symptoms suggestive of these reactions occur, Optalgin® Teva 1 g/2 ml solution for injection should be discontinued immediately and dipyrone must not be resumed at any stage (see section 4.3).

Hypotensive reactions
Dipyrone can trigger hypotensive reactions (see also section 4.8). These reactions are possibly dose-dependent. They are more likely in the case of parenteral than with enteral administration. The risk of such reactions is also higher in:
- the case of too rapid intravenous injection (see section 4.2),

- patients with, for example, pre-existing hypotension, volume depletion or dehydration, unstable circulation or incipient circulatory failure (e.g. patients with myocardial infarction or multiple injuries),
- patients with a high fever.

Careful verification of the indication (see also section 4.3) and close monitoring are therefore necessary in these patients. Preventive measures (e.g., stabilisation of the circulation) may be necessary to reduce the risk of hypotensive reactions.

Dipyrone may be used only with careful monitoring of the haemodynamic parameters in patients in whom a fall in blood pressure must be avoided at all costs, e.g. in severe coronary heart disease or relevant stenoses of the blood vessels supplying the brain.

Drug-induced liver damage
Cases of acute hepatitis with a predominantly hepatocellular pattern occurring within a few days to a few months of the start of treatment have been reported in patients treated with dipyrone . The signs and symptoms include raised serum levels of liver enzymes with or without jaundice, often in association with other drug hypersensitivity reactions (e.g., rash, blood count abnormalities, fever and eosinophilia) or accompanied by features of autoimmune hepatitis. Most patients recovered after the discontinuation of dipyrone treatment. In isolated cases, however, progression to acute liver failure with the need for liver transplantation has been reported.

The mechanism of dipyrone -induced liver damage has not been clearly elucidated. However, the data suggest an immunoallergic mechanism.

Patients should be told to consult their doctor if they develop symptoms that suggest liver damage. Treatment with dipyrone should be discontinued in such patients and hepatic function checked.

Dipyrone should not be administered again if liver damage has previously occurred on treatment with dipyrone for which no other cause could be found.

Impaired renal or hepatic function
The risks should be weighed rigorously against the benefits and appropriate precautions taken before Optalgin® Teva 1 g/2 ml solution for injection is used in patients with renal or hepatic dysfunction (see section 4.2).

Other components
One ampoule contains 65 mg sodium, equivalent to 3.3% of the 2g WHO-recommended maximum daily sodium dietary intake for adults. This must be borne in mind for people on a sodium-controlled (low sodium/salt) diet.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic induction of metabolic enzymes:
Dipyrone can induce metabolic enzymes including CYP2B6 and CYP3A4. The concomitant use of dipyrone with bupropion, efavirenz, methadone, valproate, ciclosporin, tacrolimus or sertraline can bring about a reduction in the plasma concentration of these medicinal products, with a potential decrease in clinical efficacy. Caution is therefore required in the case of co-administration with dipyrone; the clinical response and/or active substance levels should be monitored accordingly.

If dipyrone and chlorpromazine are co-administered, severe hypothermia can occur.

The concomitant administration of dipyrone with methotrexate can potentiate the haematotoxicity of methotrexate, especially in elderly patients. This combination should therefore be avoided.

Dipyrone, if co-administered, can reduce the effect of aspirin on platelet aggregation. Dipyrone should therefore be used with caution in patients who are taking low-dose aspirin for cardioprotection.

It is known of the pyrazolone substance class that interactions can occur with oral anticoagulants, captopril, lithium and triamterene, as well as changes in the efficacy of antihypertensives and diuretics. It is not known to what extent dipyrone has these interactions.

Effect on test methods
Interference with laboratory diagnostic tests based on the Trinder reaction or Trinder-like reactions (e.g., determination of serum creatinine, triglyceride, HDL-cholesterol or uric acid levels) have been reported in patients on treatment with dipyrone.

Possible interaction between dipyrone and diagnostics marketed by Teva Medical (Beckman):
1. Enzymatic Creatinine
2. Cholesterol
3. Triglyceride
4. Uric acid
5. Lactase
6. Lipase

The possible interaction is significantly lower results than the real values in patients treated by dipyrone prior to undergoing the above testing. In case any of those tests have to be performed, dipyrone has to be administered after the testing.

4.6 Pregnancy and lactation

Pregnancy
There are insufficient data for the use of dipyrone in pregnant women. Dipyrone crosses the placenta. Dipyrone did not show any teratogenic effects in animal studies (see section 5.3).
As sufficient data for humans are not available, dipyrone should be used during pregnancy only after a rigorous risk-benefit assessment by a doctor.
Although dipyrone is only a weak inhibitor of prostaglandin synthesis, the possibility of premature closure of the ductus arteriosus (Botallo's duct) and of perinatal complications resulting from a reduction in foetal and maternal platelet aggregability cannot be ruled out. The use of dipyrone in the third trimester (after week 28) should be limited to cases which do not respond to the use of paracetamol and used at the lowest effective dose.

Lactation
Dipyrone metabolites are excreted in breast milk. The use of dipyrone should be limited to cases which do not respond to the use of paracetamol or ibuprofen.

4.7 Effects on ability to drive and use machines

In the recommended dose range, no impairment of concentration and reaction speeds is known. Nevertheless, as a precaution, the possibility of impairment should be considered, at least in the case of higher dosages, and the use of machines, driving or other dangerous activities should be avoided. This applies particularly if the product is taken with alcohol.

4.8 Undesirable effects

The frequency of undesirable effects is stated on the basis of the following categories:

Very common	≥ 1/10
Common	≥ 1/100, < 1/10
Uncommon	≥ 1/1000, < 1/100
Rare	≥ 1/10,000, < 1/1000
Very rare	≤ 1/10,000
Not known	Frequency cannot be estimated from the available data

Blood and lymphatic system disorders

Rare: Leucopenia.

Very rare: Agranulocytosis, including cases with a fatal outcome, thrombocytopenia.

Not known: Aplastic anaemia, pancytopenia, including cases with a fatal outcome.

These reactions can occur even if dipyrone has previously been administered without complications (see section 4.4).

Immune system disorders

Rare: Anaphylactoid or anaphylactic reactions*.

Very rare: Analgesic-induced asthma syndrome.
In patients with analgesic asthma syndrome, intolerance reactions typically appear in the form of asthma attacks.

Not known: Anaphylactic shock*.

*These reactions can occur especially after parenteral administration, can be serious and life-threatening, and in some cases have a fatal outcome. They can occur even if dipyrone has previously been administered without complications.

Such reactions can develop during the injection or immediately after ingestion, but also hours later. However, in the majority of cases, they occur during the first hour after administration. Milder reactions typically manifest as skin and mucous membrane reactions (e.g., itching, burning, reddening, urticaria, swelling), dyspnoea and rare gastrointestinal symptoms. Milder reactions of this kind can transition into more severe forms with generalised urticaria, severe angio-oedema (including laryngeal), severe bronchospasm, arrhythmias, hypotension (sometimes preceded by a rise in blood pressure) or circulatory shock.

At the first signs of shock such as: e.g. cold sweat, dizziness, drowsiness, skin discoloration or problems in the heart area, emergency measures should be taken.

Cardiac disorders

Not known: Kounis syndrome.

Vascular disorders

Uncommon: Hypotensive reactions during or after administration which are possibly pharmacological in origin and not accompanied by other signs of an anaphylactoid or anaphylactic reaction. Such a reaction can lead to severe hypotension. Rapid intravenous injection increases the risk of a hypotensive reaction.

Even in cases of hyperpyrexia, dose-dependent critical hypotension can occur without other signs of a sensitivity reaction.

Gastrointestinal disorders

Not known: Cases of gastrointestinal bleeding have been reported.

Hepatobiliary disorders
Not known: Drug-induced liver damage including acute hepatitis, jaundice, raised liver enzymes (see section 4.4).

Skin and subcutaneous tissue disorders

Uncommon:	Fixed drug eruption.
Rare:	Rash (e.g. maculopapular rash).
Very rare:	Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) (see section 4.4).
Not known:	Drug reaction with eosinophilia and systemic symptoms (DRESS, see section 4.4).

Renal and urinary disorders

Very rare:	Acute deterioration of kidney function in which, very rarely, proteinuria, oligo- or anuria or acute kidney failure can develop; acute interstitial nephritis.

General disorders and administration site conditions
If the product is injected, pain and local reactions, and very rarely even phlebitis, can occur at the injection site.

Red discoloration of the urine has been reported; this may be caused by the harmless dipyrone metabolite rubazonic acid, which is present at a 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
http://sideeffects.health.gov.il/

4.9 Overdose

Symptoms of overdose:
Nausea, vomiting, abdominal pain, impairment of kidney function/acute kidney injury (e.g., in the form of interstitial nephritis) and – more rarely – central-nervous symptoms (dizziness, drowsiness, coma, convulsions) and hypotension, to the extent of shock and tachycardia, have been observed in the context of acute overdose.
After very high doses, the excretion of rubazonic acid can cause red discoloration of the urine.

Treatment in cases of overdose:
There is no known specific antidote to dipyrone. If the ingestion of dipyrone has only recently occurred, an attempt can be made to limit absorption into the body through primary detoxification measures (e.g., gastric lavage) or measures to reduce absorption (e.g., activated charcoal). The main metabolite (4-N-methylaminoantipyrine) can be eliminated by haemodialysis, haemofiltration, haemoperfusion or plasma filtration.
Treatment of intoxication, like the prevention of serious complications, can also require general and specialist intensive care monitoring and treatment.

Emergency treatment of serious hypersensitivity reactions (shock):
At the first signs of hypersensitivity reactions (e.g. skin reactions such as urticaria and flushing, agitation, headache, sweating, nausea) dipyrone must be discontinued. Leave the cannula in the vein,

or create a venous access. In addition to standard emergency measures such as the head-down position, keeping the airways clear, and administering oxygen, the administration of sympathomimetics, volume replacement or glucocorticoids may be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: analgesics; other analgesics and antipyretics; pyrazolones
ATC code: N02BB02

Dipyrone is a pyrazolone derivative and has analgesic, antipyretic and spasmolytic properties. The mechanism of action has not been fully explained. Some study results show that dipyrone and its main metabolite (4-N-methylaminoantipyrine) probably have a central as well as a peripheral mechanism of action.

5.2 Pharmacokinetic properties

After oral administration, dipyrone is completely hydrolysed to the pharmacologically active 4-N-methylaminoantipyrine (MAA). The bioavailability of MAA is approximately 90% and is somewhat higher after oral administration than after parenteral administration. Taking the product with meals has no relevant influence on the kinetics of dipyrone.

The main metabolite of dipyrone, MAA, is further metabolised in the liver through oxidation and demethylation, followed by acetylation.

Its clinical efficacy is based mainly on MAA, and to a certain extent also on the metabolite 4-aminoantipyrine (AA). The AUC values for AA are approximately 25% of the AUC values for MAA. The metabolites 4-N-acetylaminoantipyrine (AAA) and 4-N-formylaminoantipyrine (FAA) appear to be pharmacologically inactive.

It must be noted that all metabolites have non-linear pharmacokinetics. It is not known whether this phenomenon has any clinical significance. The accumulation of metabolites is of little importance in short-term treatment.

Dipyrone crosses the placenta. Dipyrone metabolites are excreted in breast milk.

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

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

<u>Elderly patients and patients with hepatic dysfunction</u>
The AUC increases 2- to 3-fold, in the treatment of elderly patients. After a single oral dose, the half-life of MAA and FAA increased approximately threefold in patients with cirrhosis of the liver, whereas the half-life of AA and AAA did not increase to the same extent. High doses should be avoided in these patients.

Children and adolescents
Children display more rapid elimination of the metabolites than adults.
Renal impairment
The data available from 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.

5.3 Preclinical safety data

Subchronic and chronic toxicity studies in various animal species are available. Rats received 100 to 900 mg dipyrone per kg BW 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 30 to 600 mg per kg BW for 6 months. At doses of 300 mg per kg BW and higher, dose-dependent haemolytic anaemia and dose-dependent changes in renal and hepatic function were observed.

Contradictory results from *in vitro* and *in vivo* mutagenicity studies exist for dipyrone in the same test systems.

Long-term studies in rats did not yield any evidence of carcinogenic potential. In two out of three long-term studies in mice, an increase in hepatocellular adenomas was observed at high doses.

Embryotoxicity studies in rats and rabbits did not yield any evidence of teratogenic effects.

Embryolethal effects were observed in rabbits from a daily dose of 100 mg per kg BW, which was not yet toxic to the mothers. Embryolethal effects occurred in rats at doses in the maternally toxic range. Daily doses above 100 mg per kg BW led to prolonged gestation and impairment of the birth process in rats, with increased mortality of mothers and young.

Fertility tests showed a slightly reduced gestation rate in the parent generation at doses above 250 mg per kg BW per day. The fertility of the F1 generation was not affected.

Dipyrone metabolites pass into the mother’s milk. There is no experience of their effects on the suckling young.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

6.2 Incompatibilities

Because incompatibilities are possible, it is recommended that the solution for injection should not be injected or infused mixed with other therapeutic agents.

6.3 Shelf life

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

6.4 Special precautions for storage

Store in a cool place, below 25ºC.

6.5 Nature and contents of container

Carton box containing 10 brown glass ampoules.
Each ampoule contains 2 ml solution.

6.6 Special precautions for disposal and other handling

No special requirements.

Licence Holder and Manufacturer

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