

SUMMARY OF PRODUCT CHARACTERISTICS

Optalgin[®] Caplets Optalgin[®] Tablets

1. NAME OF THE MEDICINAL PRODUCT

Optalgin[®] Caplets
Optalgin[®] Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Optalgin Caplets

Each caplet contains 500 mg Dipyrone (Metamizole sodium).

Optalgin Tablets

Each tablet contains 500 mg Dipyrone (Metamizole sodium).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Caplets

Optalgin caplets are white to creamy, oblong film coated caplets, scored on one side. The caplet can be divided into equal halves.

Tablets

Optalgin tablets are white to off-white, round flat beveled tablets with a score line on one side and engraved "TEVA" on the other side. The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Relief of moderate to severe pain as in headache, toothache, dysmenorrhea, and for 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 Optalgin.

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

Adults

1-2 caplets or 1-2 tablets up to 4 times daily.

Do not exceed 8 caplets or 8 tablets daily.

Depending on the maximum daily dose, the single dose can be taken in intervals of 6 to 8 hours.

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

Children and infants

Other pharmaceutical forms are available that allow for adequate dosing in young children and infants such as Optalgin drops.

Elderly patients

The dose should be reduced in the elderly, since elimination of the metabolites of Optalgin may be prolonged.

Debilitated patients and patients with reduced creatinine clearance

The dose should be reduced in debilitated patients and in patients with reduced creatinine clearance, since elimination of the metabolites of Optalgin may be prolonged.

Impaired kidney or liver function

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

Method of administration

The tablets are to be swallowed completely with sufficient liquid (e.g., a glass of water).

Duration of use

The duration of use depends upon the type and severity of the disease. In the event of longer-term treatment with Optalgin, regular monitoring of blood count is required, including differential blood count.

4.3. Contraindications

- Hypersensitivity to the active substance Dipyron (metamizole), other pyrazolones or pyrazolidines (this also includes patients who have developed agranulocytosis following use of such substances), or to any of the excipients listed in section 6.1.
- Patients with known analgesic-asthma-syndrome or analgesic-intolerance of urticaria-angioedema type, i.e., patients who react to salicylates, paracetamol or other non-narcotic analgesics (e.g., diclofenac, ibuprofen, indomethacin, naproxen) with bronchospasm or other anaphylactoid symptoms (e.g., urticaria, rhinitis, angioedema).
- Bone marrow failure (e.g., after treatment with cytostatics) or hematopoietic disorders.
- Acute intermittent hepatic porphyria (risk of triggering an attack of porphyria).
- In children under 4 years of age or in patients with a body weight of less than 16 kg.

4.4 Special warnings and precautions for use

Optalgin contains the pyrazolone derivative Dipyron and are associated with rare but life-threatening risks of shock and agranulocytosis (see section 4.8).

Patients who experience anaphylactoid reactions to Dipyron are at particular risk of experiencing similar reactions to other non-narcotic analgesics.

Patients who experience an anaphylactic reaction or other immunologically mediated reaction to Dipyron (e.g., agranulocytosis) are at particular risk of experiencing similar reactions 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 Optalgin.

Agranulocytosis

The treatment must be suspended immediately as soon as neutropenia ($<1,500$ neutrophils/mm³) occurs and the full blood count monitored until it returns to normal.

Patients should be instructed to stop using this medicinal product immediately if the following signs and symptoms occur and to seek medical advice: unexpected deterioration in their general condition (such as fever, chills, sore throat, difficulty swallowing), refractory or recurrent fever and painful mucosal changes, especially in the region of the mouth, nose and throat or in the genital or anal region.

The use of Optalgin must be stopped immediately and the blood count (including differential blood count) checked. Treatment must be discontinued even before laboratory test results become available (see section 4.8).

Thrombocytopenia

If signs of thrombocytopenia occur, such as an increased bleeding tendency and petechiae on the skin and mucosae (see section 4.8), administration of Optalgin must be discontinued immediately and blood count (including differential blood count) must be monitored. Treatment must be discontinued even before laboratory test results become available.

Pancytopenia

If pancytopenia occurs, treatment must be discontinued immediately and complete blood count must be monitored until it normalizes (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., malaise, infection, persistent fever, bruising, bleeding, pallor).

Anaphylactic/anaphylactoid reactions

The risk of potentially severe anaphylactoid reactions to Optalgin is significantly increased in patients with:

- Analgesic-asthma-syndrome or analgesic-intolerance of urticaria-angioedema type (see section 4.3).
- Bronchial asthma, particularly with concurrent rhinosinusitis and nasal polyps.
- Chronic urticaria.
- Intolerance to coloring agents (e.g., tartrazine) or preservatives (e.g., benzoates).
- Alcohol intolerance. Such patients react to even minimal amounts of alcohol with symptoms such as sneezing, watery eyes and severe flushing. Alcohol intolerance of this kind may be indicative of as yet undiagnosed analgesic-asthma-syndrome (see section 4.3).

Anaphylactic shock may occur, primarily in susceptible patients. Special care should therefore be taken when administered to patients with asthma or atopy.

The patient must be asked about this before the administration Optalgin. In patients with an increased risk of anaphylactoid reactions, Optalgin may be used only after carefully weighing up the possible risks against the expected benefit (see also section 4.3). If Optalgin 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, dipyrone should be discontinued immediately and dipyrone therapy must not be resumed at any stage (see section 4.3)

Isolated hypotensive reactions

Optalgin may induce hypotensive reactions (see also 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:

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

Careful indication testing and close monitoring are therefore required in such patients. Preventive measures (e.g., circulatory stabilization) may be required to reduce the risk of hypotensive reactions.

Optalgin should only be used with careful monitoring of hemodynamic parameters in patients in whom a reduction in blood pressure must be avoided at all costs, e.g., patients with severe coronary heart disease or relevant cerebrovascular stenosis.

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 immune-allergic 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 is used in patients with renal or hepatic dysfunction (see section 4.2).

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, cyclosporine, 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 metamizole; the clinical response and/or active substance levels should be monitored accordingly.

Severe hypothermia may develop following concomitant use of Optalgin and chlorpromazine.

Co-administration of Dipyrone and methotrexate may increase the hematotoxicity of methotrexate, especially in elderly patients. This combination should therefore be avoided.

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

The pyrazolones are known to interact with oral anticoagulants, captopril, lithium and triamterene, and to cause potential changes in the effectiveness of antihypertensives and diuretics. It is not known to what extent Dipyron also triggers such interactions.

Effect on test methods

There have been reports of Dipyron interference with Trinder and Trinder-like reaction assays (e.g., determination of serum levels of creatinine, triglyceride, HDL cholesterol or uric acid). Therefore, In cases of these tests the patient should take Optalgin only after giving a blood sample.

4.6. Pregnancy, breast-feeding and fertility

Pregnancy

There are no adequate data from the use of Dipyron in pregnant women. Dipyron crosses the placental barrier. Dipyron has not been associated with teratogenic effects in animal studies (see section 5.3).

Although Dipyron is a weak inhibitor of prostaglandin synthesis, the possibility of premature closure of the ductus arteriosus (Botalli) and perinatal complications due to a reduction in platelet aggregability in the mother and child cannot be excluded.

The use of Dipyron in the third trimester (after week 28) should be used at the lowest effective dose. The daily dose should be up to 3 grams, for only 3-4 days. Longer treatment needs close medical supervision

Breast-feeding

The metabolites of Dipyron are excreted in breast milk. The use of Dipyron 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

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 of the ability to concentrate and react should be taken into account, and patients should avoid using machines, driving or other hazardous activities. This applies particularly in conjunction with alcohol.

4.8 Undesirable effects

The frequency of adverse reactions is defined using the following convention:

Very common	$\geq 1/10$
Common	$\geq 1/100, < 1/10$
Uncommon	$\geq 1/1,000, < 1/100$
Rare	$\geq 1/10,000, < 1/1,000$
Very rare	$\leq 1/10,000$
Not known	Frequency cannot be estimated from available data

Blood and Lymphatic System Disorders

Rare: Leukocytopenia.
Very rare: Agranulocytosis (including fatal cases), thrombocytopenia.
Not known: Aplastic anemia, pancytopenia (including fatal cases).

These reactions can occur even if Dipyron was previously administered without complications.

There are isolated reports suggesting that the risk of agranulocytosis may possibly be increased if Dipyron is used for longer than a week.

This reaction is not dose-dependent and can occur at any time during treatment. It is manifested by high fever, chills, sore throat, dysphagia and inflammation of the mouth, nose, throat and genital or anal area. These signs may be minimal, however, in patients receiving antibiotics. There is little or no swelling of the lymph nodes or spleen. Erythrocyte sedimentation rate is significantly accelerated, whilst granulocytes are considerably reduced or completely absent. Hemoglobin, erythrocyte and platelet values are generally, but not always, normal (see section 4.4).

Immediate discontinuation is essential for recovery. **Therefore, optalgin treatment must be discontinued immediately**, without waiting for the results of laboratory-diagnostic tests, in the event of unexpected deterioration in general condition, persistent or recurrent fever, or painful mucosal changes (especially in the mouth, nose and throat region).

Typical signs of thrombocytopenia include an increased bleeding tendency and petechiae on the skin and mucosae.

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

Immune System Disorders

Rare:

Anaphylactoid or anaphylactic reactions*.

Very rare:

Analgesic-asthma-syndrome

In patients with analgesic-asthma-syndrome, intolerance reactions are typically manifested in the form of asthma attacks.

Frequency Not known:

Anaphylactic shock*.

*These reactions may occur in particular following parenteral application and may be severe and life-threatening, in some cases even fatal. They can also occur if Dipyron was previously administered without complications.

Such reactions may occur during injection or immediately after administration, but may also develop hours later. In the majority of cases, however, they develop within the first hour of administration. Milder reactions are typically manifested in the form of skin and mucosal reactions (e.g., itching, burning sensation, redness, urticaria, swelling), dyspnea and (in rarer cases) gastrointestinal complaints. Such milder reactions may become more severe, progressing to generalized urticaria, severe angioedema (also in the laryngeal region), severe bronchospasm, cardiac arrhythmias, hypotension (sometimes with preceding hypertension) and circulatory shock.

Optalgin should therefore be discontinued immediately in the event of skin reactions.

Cardiac disorders

Frequency 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 reactions can lead to severe hypotension. Rapid intravenous injection increases the risk of hypotensive reactions.

Dose-dependent critical hypotension may also occur in the event of hyperpyrexia, without further signs of hypersensitivity.

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 exanthema).

Very rare: Stevens-Johnson syndrome or toxic epidermal necrolysis, 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 renal function, which may progress in very rare cases to proteinuria, oliguria or anuria, or acute renal failure, acute interstitial nephritis.

General disorders and administration site conditions

There have been reports of red urine discoloration, which may be attributable to the harmless Dipyrone metabolite, rubazonic acid, present at low concentrations.

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: <https://sideeffects.health.gov.il>

4.9 Overdose

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 hypotension, progressing to shock and tachycardia, have been observed following acute overdose. After very high doses, excretion of rubazonic acid may cause red discoloration of the urine.

Therapeutic measures following overdose:

No specific antidote is known for Dipyrone. If the Dipyrone was only recently taken, attempts can be made to limit systemic absorption using primary detoxification measures (e.g., gastric lavage) or absorption-reducing measures (e.g., activated charcoal). The main metabolite (4-N-methylaminoantipyrine) can be eliminated by hemodialysis, hemofiltration, hemoperfusion or plasma filtration.

Treatment of intoxication and prevention of severe complications may require general and specialist intensive care monitoring and treatment.

Emergency measures in the event of severe hypersensitivity reactions (shock):

At the first signs (e.g., skin reactions such as urticaria and flushing, agitation, headache, sweating, nausea) stop administration. Leave cannula in situ or establish venous access. In addition to standard emergency measures such as Trendelenburg positioning, maintenance of patent airways and administration of oxygen, the administration of sympathomimetics, volume expanders 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 is not fully understood. Some research findings suggest that Dipyrone and the main metabolite (4-N-methylaminoantipyrine) may have both a central and a peripheral mechanism of action.

5.2 Pharmacokinetic properties

After oral administration, Dipyrone is completely hydrolyzed to the pharmacologically active 4-N-methylaminoantipyrine (MAA). The bioavailability of MAA is approx. 90% and is slightly higher after oral administration than after parenteral administration. Concomitant intake of food does not have a relevant effect on Dipyrone kinetics.

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

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

It should be noted that all of the metabolites display non-linear pharmacokinetics. The clinical significance of this phenomenon is unknown. Accumulation of the metabolites is of little significance with short-term treatment.

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

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

Dipyrone's plasma half-life following intravenous administration is approx. 14 minutes. After intravenous administration approx. 96% of a radiolabeled dose is recovered in the urine and approx. 6% in the feces. Following a single oral dose, 85% of the urinary metabolites excreted were identified. Of this percentage, MAA accounted for 3±1%, AA 6±3%, AAA 26±8% and FAA 23±4%. Renal clearance after a single oral dose of 1 g Dipyrone was 5±2 mL/min for MAA, 38±13 mL/min for AA, 61±8 mL/min for AAA and 49±5 mL/min for FAA. The associated plasma half-lives 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.

Elderly patients and patients with hepatic dysfunction

The AUC is 2 to 3 times higher with treatment of elderly patients. Following a single oral administration, the half-life of MAA and FAA increased approx. 3-fold in patients with hepatic cirrhosis, whereas the half-lives of AA and AAA did not increase to the same extent. High doses should be avoided in such patients.

Children and adolescents

Children display more rapid elimination of the metabolites than adults do.

Renal impairment

The data available for patients with renal impairment indicate a reduced elimination rate for some metabolites (AAA and FAA). High doses should therefore be avoided in such patients.

5.3 Preclinical safety data

Subchronic and chronic toxicity studies have been performed on various animal species. Rats were orally administered with Dipyron at doses of 100 mg to 900 mg/kg body weight for 6 months. At the highest dose (900 mg/kg body weight), an increase in reticulocytes and Heinz bodies was observed after 13 weeks.

Dogs were administered with Dipyron at doses of 30 to 600 mg/kg body weight for 6 months. Dose-dependent hemolytic anemia and changes in renal and hepatic function have been observed from 300 mg/kg body weight.

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

Long-term studies in rats have not produced any evidence of tumorigenic potential. Increased liver cell adenomas were observed at high doses in two out of three long-term studies in mice.

Embryo toxicity studies in rats and rabbits have not revealed any evidence of teratogenic effects.

Embryolethal effects have been observed in rabbits from a non-maternally toxic daily dose of 100 mg/kg body weight. In rats, embryolethal effects only occurred at doses in the maternally toxic range. Daily doses in excess of 100 mg/kg body weight led to prolonged gestation in rats and impaired parturition with increased maternal and pup mortality.

Fertility tests revealed a slightly decreased pregnancy rate in the parental generation at doses above 250 mg/kg body weight/day. The fertility of the F1 generation was not affected.

The metabolites of Dipyron are excreted in breast milk. There is no experience with regard to their effects on suckling pups.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Optalgin Caplets:

Starch, gelatin, magnesium stearate, talc, colloidal silicon dioxide, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, polysorbate 80.

Optalgin Tablets:

Starch, gelatin, magnesium stearate, talc, colloidal silicon dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Optalgin caplets in a bottle: after first opening, the product can be used until the expiry date.

6.4 Special precautions for storage

Optalgin caplets/ tablets: Store in a dry place, below 25°C.

6.5 Nature and contents of container

Optalgin Caplets: Pack containing 21, 28 or 42 caplets in blisters or bottle containing 50 caplets.
Optalgin Tablets: Pack containing 20 tablets in blisters.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 LICENCE HOLDER AND MANUFACTURER

TEVA ISRAEL LTD.,
124 Dvora HaNevi'a St., Tel Aviv 6944020, Israel

8 REGISTRATION NUMBER

Optalgin Caplets: 066.25.27767
Optalgin Tablets: 016.87.20611

The leaflet was revised in June 2022 in accordance with the MoH guidelines.