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.

4.3. Contraindications

- Hypersensitivity to the active substance Dipyrone (metamizole), other pyrazolones or pyrazolidines, or to any of the excipients listed in section 6.1.
- Agranulocytosis in the medical history induced by metamizole, other pyrazolones or pyrazolidines
- 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).
- Impaired bone marrow function or diseases of the hematopoietic system.
- 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

Agranulocytosis
Treatment with metamizole can cause agranulocytosis, which may be fatal (see section 4.8). It may occur even after metamizole has previously been used without complications.
Metamizole-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 mouth, nose and throat or in the genital or anal region).
If metamizole 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 results. If confirmed, treatment must not be reintroduced (see section 4.3).

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

Patients who experience anaphylactoid reactions to Dipyrone 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 Dipyrone (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.

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.

Dipyrone, if co-administered, can reduce the effect of aspirin on platelet aggregation. Dipyrone 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 Dipyrone also triggers such interactions.

Effect on test methods
There have been reports of Dipyrone 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 Dipyrone in pregnant women. Dipyrone crosses the placental barrier. Dipyrone has not been associated with teratogenic effects in animal studies (see section 5.3).

Although Dipyrone 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 Dipyrone 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 Dipyrone 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

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	≥ 1/10
Common	≥ 1/100, < 1/10
Uncommon	≥ 1/1,000, < 1/100
Rare	≥ 1/10,000, < 1/1,000
Very rare	≤ 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 Dipyrone was previously administered without complications.

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 Dipyrone 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. 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.

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).**

** Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in association with metamizole treatment (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 Dipyrone 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 Dipyrone 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 Dipyrone 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 Dipyrone 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 May 2025 in accordance with the MoH guidelines.