SUMMARY OF PRODUCT CHARACTERISTICS

OPTALGIN® DROPS NEW

1. NAME OF THE MEDICINAL PRODUCT

OPTALGIN® DROPS NEW
Oral drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml (20 drops) contains 500 mg Dipyrone (Metamizole sodium)
1 drop contains 25 mg Dipyrone (Metamizole sodium).

Excipients with known effect:
This medicinal product contains 37.5 mg sodium, approx. 10 mg propylene glycol and approx. 0.2 mg benzyl alcohol per 1 ml solution.

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Oral drops, solution.

Clear, slightly yellow to yellow-green solution.

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 Drops New.* It is essential to use the lowest dose that effectively relieves pain and reduces fever.

The oral drops are taken with a little bit of water.
Depending on the maximum daily dose, the single dose can be taken in intervals of 6 to 8 hours.

Adults and Adolescents from 15 Years Old (over 53 kg body weight) :
20-40 drops up to 3 times daily.

Infants and Children:
For all age groups except babies, 8-16 mg of Dipyrone per kg body weight can be administered as a single dose. The table below shows the recommended single dose and the maximum daily dose as a function of body weight or age.

Age	Body weight (kg)	Dose in Number of drops (Dose in mg)
3-11 months	5-8 kg	2-4 drops, up to 3 times daily (50 – 100 mg)
1-3 years	9-15 kg	3-10 drops, up to 3 times daily (75 – 250 mg)
4-6 years	16-23 kg	5-15 drops, up to 3 times daily (125 – 375 mg)
7-9 years	24-30 kg	8-20 drops, up to 3 times daily (200 – 500 mg)
10-12 years	31-45 kg	10-30 drops, up to 3 times daily (250 – 750 mg)
13-14 years	46-53 kg	15-35 drops, up to 3 times daily (375 – 875 mg)

Special patient populations

Elderly patients, patients in reduced general health, and patients with impaired creatinine clearance:

In elderly patients, patients in reduced general health and patients with impaired creatinine clearance, the dose should be reduced as the elimination of Dipyrone metabolites may be prolonged.

Impaired kidney and 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 adequate experience with long-term use of Dipyrone in patients with severe renal and/or hepatic impairment.

Method of administration

It is recommended to take the drops with 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,benzyl alcohol, or to any of the excipients listed in section 6.1.
- Agranulocytosis in the medical history induced by metamizole, other pyrazolones or pyrazolidines
- Patients diagnosed with 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 patients with a body weight less than 5 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 Drops contains the pyrazolone derivative Dipyrone (Metamizole) and are associated with rare but life-threatening risks of shock and agranulocytosis (see section 4.8).

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

Patients who experience an anaphylactic reaction or another immunologically mediated reaction to *Optalgin* (e.g., agranulocytosis) are also at particular risk of experiencing similar reactions to other pyrazolones and pyrazolidines.

Patients who experience anaphylactic or another immunologically mediated reaction to other pyrazolones, pyrazolidines or other non-narcotic analgesics are also at particular risk of experiencing similar reactions to *Optalgin* Drops.

Thrombocytopenia
If signs of thrombocytopenia occur, such as increased tendency to bleed or petechiae on the skin and mucous membranes (see section 4.8), the use of Optalgin Drops must be immediately interrupted and the blood count (including differential blood count) monitored. Discontinuation of treatment must not be withheld until laboratory test results are 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
When selecting the route of administration, it should be taken into account that parenteral administration of Optalgin Drops is associated with a higher risk of anaphylactic and 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).

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

Patients should be questioned accordingly prior to the administration of Optalgin Drops. In patients at increased risk of anaphylactoid reactions, Optalgin Drops should be used only after carefully weighing up potential risks against the expected benefit (see also section 4.3). If Optalgin Drops is administered in such cases, the patient should be closely monitored medically and emergency facilities should be available.

Severe cutaneous 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 with Dipyrone therapy.

Patients should be advised of 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).

Drug-induced liver injury

Cases of acute hepatitis of predominantly hepatocellular pattern have been reported in patients treated with metamizole with an onset of few days to few months following treatment initiation. Signs and symptoms include elevated serum hepatic enzymes with or without jaundice, frequently in context of other drug hypersensitivity reactions (e.g. skin rash, blood dyscrasias, fever and eosinophilia) or accompanied by features of autoimmune hepatitis. Most patients recovered on discontinuation of metamizole treatment; nevertheless, in isolated cases, progression to acute liver failure requiring liver transplantation was reported.

The mechanism of metamizole-induced liver injury is not clearly elucidated, but data indicate an immuno-allergic mechanism.

Patients should be instructed to contact their doctor in case symptoms suggestive of liver injury occur. In such patients metamizole should be discontinued and liver function should be assessed.

Metamizole should not be re-introduced in patients with an episode of hepatic injury during treatment with metamizole for which no other cause of liver injury has been determined.

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:
- 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., in patients with myocardial infarction or multiple trauma);
- Patients with high fever.

The indication should therefore be carefully established in such patients and they should be closely monitored.. Preventive measures (e.g., circulatory stabilization) may be required to reduce the risk of hypotensive reactions.

Optalgin Drops may be administered only if hemodynamic parameters are closely monitored 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.

Optalgin Drops should be only used after careful consideration has been given to the benefit versus risk ratio and only if appropriate precautions are taken in patients with impaired renal or hepatic function (see section 4.2).

Excipients:

- Sodium
  Optalgin drops contains 37.5 mg sodium per 1 ml, equivalent to 1.9% of the maximum daily dietary sodium intake of 2 g recommended by the WHO for an adult.

- Benzyl alcohol
  Benzyl alcohol has been associated with the risk of serious side effects including breathing problems (called "gasping syndrome") in infants and toddlers. The medicinal product should not be used for more than a week in infants and toddlers (under 3 years old) because of accumulation. Large quantities of benzyl alcohol should be used with caution and only when absolutely necessary because of the risk of accumulation and toxicity (metabolic acidosis), particularly in people with impaired hepatic or renal function, and during pregnancy and lactation.

- Propylene glycol
  This medicinal product should be used with caution in infants under 4 weeks old, particularly if they are also receiving other medicinal products containing propylene glycol or alcohol.

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 Dipyrone; 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.

When used concomitantly, Dipyrone may reduce the effects of **acetylsalicylic acid** . Dipyrone therefore should be used with caution in patients taking low-dose acetylsalicylic acid for cardioprotection.

The pyrazolones class of active substances has a known potential to cause interactions with oral **anticoagulants, captopril, lithium** and **triamterene** to influence the efficacy of antihypertensives agents and diuretics. It has been established how far metamizole leads to these interactions.

Influence on diagnostic measures

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 and breast-feeding

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 in particular 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.
Nnot 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.

Cardiac disorders

Not known:	Kounis syndrome.

Vascular disorders

Uncommon:	Hypotensive reactions during or after administration, which may be pharmacologically induced and may not be accompanied by other signs of 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 haemorrhage 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 (discontinue treatment.
Not known:	Drug reaction with eosinophilia and systemic symptoms (DRESS).

Severe adverse skin reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), have been reported in connection with Dipyrone therapy (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.

Benzyl alcohol may cause allergic reactions.

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):
Stop administration at the first sign of hypersensitivity (e.g., cutaneous reactions such as urticaria and flushing, agitation, headache, sweating, nausea). 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 by 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 liver 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 show faster elimination of metabolites than adults

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 (bw) for 6 months. At the highest dose (900 mg/kg bw), 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 bw for 6 months. Dose-dependent hemolytic anemia and changes in renal and hepatic function have been observed from 300 mg/kg bw.

There are contradictory results for Dipyrone from *in vitro* and *in vivo* 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 bw. In rats, embryolethal effects only occurred at doses in the maternally toxic range. Daily doses in excess of 100 mg/kg body weight resulted in prolonged gestation in rats and impairment of the birth process resulting in increased maternal and offspring mortality.

Fertility tests revealed a slightly decreased pregnancy rate in the parental generation at doses above 250 mg/kg bw/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

Saccharin sodium, Sodium cyclamate, Flavor Raspberry (contains nature-identical flavoring substances, benzyl alcohol, flavoring preparations, propylene glycol); Flavor cream (contains nature-identical flavoring substances, triacetin, propylene glycol, benzyl alcohol); Citric acid monohydrate, sodium hydroxide, Purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Shelf life after first opening: **6 months**

6.4 Special precautions for storage

Store in a dry place, below 25°C.

6.5 Nature and contents of container

Amber glass dropper bottle (type III glass) with a (polyethylene) drop dispenser and (polypropylene) child-resistant closure.
Pack containing 10 ml, 20 ml, 50 ml, 100 ml oral drops, solution
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. LICENSE HOLDER AND MANUFACTURER

Teva Israel Ltd.,
124 Dvora HaNevi'a St., Tel Aviv 6944020, Israel

8. REGISTRATION NUMBER:

164.35.35644.00

9. DATE OF REVISION OF THE TEXT

revised in May 2025.