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)

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.
In the event of longer-term treatment with Optalgin Drops New, regular monitoring of blood count is required, including differential blood count.

4.3 Contraindications

- Hypersensitivity to the active substance, other pyrazolones or pyrazolidines (this also includes patients who have developed agranulocytosis following use of such substances),benzyl alcohol, or to any of the excipients listed in section 6.1.
- 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).
- Bone marrow failure (e.g., after treatment with cytostatics) or hematopoietic disorders.
- 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

- *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.

Agranulocytosis
If signs of agranulocytosis or thrombocytopenia (see section 4.8) occur, the use of *Optalgin* must be discontinued immediately and blood count (including the differential blood count) must be checked. 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.

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.

Patients should 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. 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 Drops 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 metamizole-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
Optalgin Drops should only be used after careful risk-benefit assessment and appropriate precautions in patients with renal or hepatic impairment (see section 4.2).

Patients should be asked relevant questions prior to administration of *Optalgin*.
Optalgin should only be used after carefully weighing the potential risks against the anticipated benefits in patients at increased risk of anaphylactoid reactions. If *Optalgin Drops* are administered in such cases, patients should be placed under close medical supervision, with emergency facilities available.

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** 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 assay 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 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.

There is isolated evidence that the risk of agranulocytosis may increase if Dipyrone is used for more than one 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. It is therefore strongly recommended to discontinue *Optalgin Drops* 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).

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.
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.

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

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: There have been reports of cases of gastrointestinal bleeding.

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 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
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.

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 or 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

The leaflet was revised in June 2022 according to the MoH guidelines.