# 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.

*Optalgin Tablets*
Each tablet contains 500 mg Dipyrone.
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*
For children and infants dosage refer to 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 renal or hepatic 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 whole 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 Dipyrone (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 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 another immunologically mediated reaction to Dipyrone (e.g., agranulocytosis) are at particular risk of experiencing similar reactions to other pyrazolones and pyrazolidines.

Agranulocytosis
If signs of agranulocytosis or thrombocytopenia occur (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.

Severe skin reactions
There have been reports of the life-threatening skin reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) following use of Dipyrone. If symptoms or signs of SJS or TEN develop (such as progressive rash, often associated with blisters or mucosal lesions), treatment with Optalgin must be discontinued immediately and not resumed at any stage.

Patients should be advised of the signs and symptoms and should be monitored closely for skin reactions, especially in the first few weeks of treatment.

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.

Optalgin 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 the 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 are administered in such cases, patients should be placed under close medical supervision, with emergency facilities available.

## 4.5 Interaction with other medicinal products and other forms of interaction

Dipyrone may cause a decrease in serum cyclosporine levels. These must therefore be monitored if Optalgin is used concomitantly.

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 may reduce the anti-platelet activity of low-dose aspirin in the event of concomitant use. Dipyrone should therefore be used with caution in patients taking low-dose aspirin for cardioprotection.

Dipyrone may reduce bupropion blood levels. Caution should therefore be exercised with concomitant administration of Dipyrone and bupropion.

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. **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).

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*

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|---|---|
| *Rare:* | Anaphylactoid or anaphylactic reactions*. |
| *Very rare:* | Analgesic-asthma-syndrome<br>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 should therefore be discontinued immediately in the event of skin reactions.

*Cardiac disorders*

| | |
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| *Frequency 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.

*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, see section 4.4). |

*Renal and urinary disorders*

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|---|---|
| *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):*
Stop administration at the first sign of hypersensitivity reactions (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 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 bw 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 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

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 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 Pharmaceutical Industries Ltd.
P.O.Box 3190, Petah Tikva

## 8 REGISTRATION NUMBER

Optalgin Caplets: 066.25.27767
Optalgin Tablets: 016.87.20611

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