Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986 This medicine is dispensed without a doctor's prescription

DULERGIN

Drops for oral administration Composition

Every 1 ml (20 drops) contains: Dipyrone 500 mg For information about inactive ingredients, see section 2 - under "Important information about some of this medicine's ingredient's" and section 6 - "Additional information

Read the entire leaflet carefully before you start using this medicine. This leaflet contains concise information about this medicine. If you have any further

leaflet contains concise information about this medicine. If you have any further guestions, consult your doctor or pharmacist. Take this medicine according to the instructions in the section about dose in this leaflet. Consult your pharmacist if you need further information. You must take it correctly. These drops are not intended for babies weighing under 5 kg. Consult your doctor if your fever lasts more than 3 days or pain persists for more than 7 days, even though you are using the medicine. There is a greater risk of agranulocytosis if treatment continues for longer than 7 days (see section 4 - "Side effects").

1. What is this medicine intended for? This medicine is intended for relieving moderate to severe pain, such as headache, toothache, and menstrual pain, and for reducing high fever that does not respond to other treatment measures. Therapeutic group: pyrazolone class

2. Before using this medicine

Do not use this medicine if:

- You are sensitive (allergic) to the active ingredient dipyrone (metamizole) or other pyrazolones (such as propyphenazone, phenazone) or pyrazolidines (such as phenylbutazone, oxyphenbutazone); this also includes patients who have, for example, developed a significant reduction in counts of certain white blood cells (agranulocytosis) after using these orbital instructions of the sensitive active ingredients.
- active ingredients. You are sensitive (allergic) to any of the other ingredients in this medicine (see section 6 "Additional information"). You have a known sensitivity to pain relievers (analgesics asthma syndrome or sensitivity to pain relievers experienced as rash/ angioedema). This applies to patients who react to pain relievers (such as salivitates, parcetamol, dickforage invortion, indomethation, par as salicylates, paracetamol, diclofenac, ibuprofen, indomethacin, or naproxen) with constriction of the lower airways or other hypersensitivity reactions such as rash with itching and bruising, runny nose and swelling (rash, rhinitis, angioedema).
- (rash, minute, angloedema).
 Your bone marrow function is impaired, for example after treatment with certain medicines used to treat cancer.
 You have a disorder affecting the production of blood cells.
 You have a hereditary disease which includes a disorder in the production of the color of your red blood cells (acute intermittent hepatic porphyria).
- Special warnings about using this medicine
 Dulergin contains dipyrone and is associated with the following rare but life-
- Dulergin contains dipyrone and is associated with the following rare but inte-threatening risks:
 sudden circulatory failure.
 agranulocytosis (a severe disease caused by a sharp drop in the count of certain white blood cells).
 Stop taking Dulergin and consult your doctor immediately if you get any of the following signs of possible agranulocytosis:
 sudden worsening of your health (for example fever, chills, throat ache, difficulty swallowing).
 fever that does not no away or fever that keeps coming back
- fever that does not go away or fever that keeps coming back. changes in mucous membranes that are associated with pain, especially in the mouth, nose and throat or in the genitals or anal area; see section 4 "Side effects".
- 4 "Side effects". If you develop signs of low counts of different types of blood cells (pancytopenia) (such as feeling generally unwell, inflammation or persistent fever, bruises, bleeding, and pallor) or signs of low platelet count (thrombocytopenia) (such as increased tendency to bleed, tiny bleeds under the skin and in mucous membranes), stop taking Dulergin immediately and consult a doctor without delay (see section 4 "Side effects"). Your doctor may monitor your bleed
- doctor may monitor your blood count regularly and stop your treatment if
- Your doctor may monitor your blood count regularly and stop your treatment if certain changes occur.
 If you develop an allergic reaction to Dulergin, you are at a high risk of developing similar reactions to other pain relievers.
 If you develop allergic reactions to other pain relievers.
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 If you develop an allergic reactions to pain relievers.
 If you develop and as agranulocytosis), you are at a high risk of developing similar reactions to other pyrazolones and pyrazolidines (substances that are chemically similar), for example the pain relievers containing phenazone, propyphenazone, phenylbutazone, and oxyphenbutazone.
 If you develop an allergic reaction to other pyrazolones and pyrazolidines medicines or to other pain relievers, or if you get another reaction mediated by the immune system, you are at a high risk of developing a similar reaction
- to Dulergin.

- to Dulergin.
 Severe hypersensitivity reactions
 If you have any of the following effects, your risk of severe hypersensitivity reactions to Dulergin is significantly increased:
 Sensitivity to pain-relief and anti-rheumatic medicines that is experienced as itchy rash and bruising or swelling. If this happens, do not take Dulergin. For additional information, see section 2 under "Do not use this medicine if".
 Attacks of breathlessness caused, for example, by asthma, particularly if you also have nasal polyps or a nose and sinus inflammation.
 Chronic rash (urticaria).
 Hypersensitivity to coloring agents (such as tartrazine) or preservatives (such as benzoates).
- as benzoates)
- as benzoates). Sensitivity to alcohol experienced as sneezing, watery eyes, and severe flushing in the face which develop after consuming even small amounts of alcohol. This kind of sensitivity to alcohol may be a sign of an as-yet undiagnosed sensitivity to pain relievers (see section 2 under "Do not use this medicine if").
- Patients at increased risk of hypersensitivity reactions, should only use Dulergin after the doctor has carefully weighed the potential risks against the expected benefit (see also section 2 under "Do not use this medicine if"). If Dulergin is used in such cases, patients should be placed under close medical supervision, with emergency facilities available. Anaphylactic shock may occur, particularly in susceptible patients (see section 4 "Side effects"). Special care is needed in patients with asthma or a tendency to develop hypersensitivity reactions.

Severe skin reactions

Severe skin reactions Severe skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (called DRESS), have been reported following dipyrone therapy. If you feel one or more of the symptoms of these severe skin reactions that are described in section 4 ("Side effects"), stop taking Dulergin and seek medical care immediately. If you have ever experienced severe skin reactions, you must not resume treatment with Dulergin again (see section 4 - "Side effects").

Drop in blood pressure Dulergin can cause a drop in blood pressure (see section 4 - "Side effects"). This risk is increased if you:

- have low blood pressure, are severely dehydrated, have poor blood circulation, or are in the early stages of circulatory failure (for example following a heart attack or severe injuries).

 have a high fever.
 Your doctor will carefully consider the use of Dulergin, will monitor the patient closely, and will take preventive measures (such as circulatory stabilization) to the start of a carefully consider the use of Dulergin may only be used with reduce the risk of a drop in blood pressure. Dulergin may only be used with careful monitoring of your blood circulation, when avoiding a drop in blood pressure is necessary. For example in case of: - serious coronary heart disease. - constriction that blocks blood flow in the vessels that supply blood to the brain.

Liver function problems There are reports of liver inflammation in patients taking dipyrone who developed symptoms within a few days to a few months of starting treatment. Stop taking Dulergin and consult your doctor if you develop symptoms of liver function problems, such as:

pelovinal, occurring, fever, tiredness, loss of appetite, dark urine, pale stools, yellowing of the skin or the whites of the eyes, itching, rash, or upper abdominal pain. Your doctor will check your liver function in these cases. Do not take Dulergin if you have ever taken a medicine containing dipyrone and

developed liver function problems. Impaired kidney or liver function

In case of impaired kidney or liver function, you may take Dulergin only after your doctor has carefully evaluated the risk and the benefit and has taken suitable precautions (see section 3 - under "Patients with impaired kidney or liver function").

Use in children

 Dulergin immediately and consult a doctor as soon as possible:
 If you suddenly develop any of the following side effects or if they get significantly worse, tell your doctor immediately. Certain side effects (such as severe hypersensitivity reactions; severe skin reactions like Stevens-Johnson syndrome, toxic epidermal necrolysis or DRESS syndrome; agranulocytosis This medicine is not intended for babies weighing less than 5 kg. See the dosage table by weight and age in section 3

Drug interactions

If you are taking or have recently taken other medicines, including nonprescription medications and dietary supplements, tell your doctor or pharmacist. Particularly if you are taking: • Cyclosporine (a medicine used to suppress the immune system) - Your doctor will monitor your blood cyclosporine levels, if you are taking it at the same time.

- Methotrexate, a medicine used to treat cancer and rheumatic diseases If given at the same time, methotrexate may increase the risk of potential damage to blood production, particularly in elderly patients. This combination should therefore be avoided.
- Acetylsalicylic acid (aspirin) If you take low-dose acetylsalicylic acid to protect your heart, Dulergin may reduce the effect of aspirin on your platelets. Bupropion, used to treat depression and to stop smoking Dulergin may reduce blood levels of bupropion.
- Chlororomazine a medicine used to treat mental disorders Using Dulergin at
- Efavirenz, a medicine used to treat HIV/AIDS. Methadone, a medicine used to treat severe pain or withdrawal from addiction

not continue taking Dulergin without medical supervision. Stopping your treatment early could have decisive importance to your recovery. If signs of agranulocytosis, pancytopenia or thrombocytopenia occur (see below and in section 2), you must stop using Dulergin immediately, and your doctor must order a blood count (including a differential blood count). Treatment must be stopped even before your laboratory test results are variable.

results are available.

feet

results are available. If you get the following symptoms, which could be signs of liver damage (see also section 2): nausea or vomiting, fever, tiredness, loss of appetite, dark urine, pale stools, yellowing of the skin or the whites of the eyes, itching, rash, or upper abdominal pain. Stop taking Dulergin and seek medical care immediately if you experience one of the following severe side effects (see also section 2): • reddish, non-elevated, target-like or circular lesions on the upper torso, generally with a blister in the middle, peeling of the skin, ulcers in the mouth, throat, nose, genitals and eyes. These severe skin rashes may be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome, toxic epidermal necrolysis). • extensive rash, high temperature and enlarged lymph nodes (DRESS

extensive rash, high temperature and enlarged lymph nodes (DRESS syndrome or drug hypersensitivity syndrome).

Syndrome or drug hypersensitivity syndrome).
 Additional side effects
 Uncommon side effects (may affect up to 1 in 100 patients):

 purple to deep red rash, sometimes with blisters (fixed drug eruption).
 sharp drop in blood pressure, which may be a direct effect of the medicine and is not accompanied by other signs of a hypersensitivity reaction. Such reactions only rarely lead to severe drop in blood pressure may be increased in case of abnormally high fever. Typical symptoms of a sharp drop in blood pressure are: rapid heartbeat, pallor, trembling, dizziness, nausea, and fainting.

 Rare side effects (may affect up to 1 in 100 patients):

 a side affects (may affect up to 1 in 100 patients):
 b sharp drop in blood pressure may be increased in case of abnormally high fever. Typical symptoms of a sharp drop in blood pressure are: rapid heartbeat, pallor, trembling, dizziness, nausea, and fainting.

Rare side effects (may affect up to 1 in 1,000 patients):
 Hypersensitivity reactions (anaphylactoid or anaphylactic reactions). Signs of milder reactions include: burning sensation in the eyes, cough, runny nose, sneezing, tightness in the chest, skin redness (especially in the face and head area), hives

and facial swelling, and less commonly nausea and abduminal cramps. Special warning symptoms include a burning, itching and heat sensation on and under the tongue and, in particular, on the hands and

feet. Such milder reactions can develop into more serious forms, including severe rash, severe angioedema (swelling, also in the throat area), severe constriction (bronchospasm) of the lower airways, fast heart beat (sometimes a slow heart beat), heart-rhythm disorders, sharp drop in blood pressure, sometimes also with a previous increase in blood pressure, unconsciousness, and circulatory failure. These reactions can still occur even if you have already taken this medicine a few times without complications. These reactions can be severe to life-threatening, and in some cases even fatal. In patients with analgesics asthma syndrome, hypersensitivity reactions are usually experienced as asthma attacks (see section 2 - under "Do not use this medicine if").

Skin rash (such as maculopapular exanthema).
 Very rare side effects (may affect up to 1 in 10,000 patients):
 Seriously reduced counts of certain white blood cells (agranulocytosis), including fatal cases, or reduces platelet count (thrombocytopenia). These reactions are probably caused by the immune system. They can also occur if you have previously taken dipyrone without complications. There is evidence that the risk of agranulocytosis is increased if Dulergin is taken for more than one week.
 Agranulocytosis is experienced as high fever, chills, sore throat, difficulty swallowing, and inflammation of the mouth, nose, throat and genital or anal area. In patients on antibiotics (medicines used to treat bacterial infections), these symptoms may be mild. The erythrocyte sedimentation rate is significantly elevated, whereas the lymph nodes are typically only slightly enlarged or not at all. Typical symptoms of low platelet count (thrombocytopenia) include an increased bleeding tendency and red pinpoint spots on the skin and mucous membranes caused by bleeding.
 Astima attack
 Extensive blistering of the skin and skin peeling (Stevens-Johnson

Astnma attack
 Extensive bilstering of the skin and skin peeling (Stevens-Johnson syndrome or toxic epidermal necrolysis).
 Sharp deterioration in kidney function, in some cases with abnormally little or no urine, excretion of blood proteins in the urine, acute kidney failure, kidney inflammation (acute interstitial nephritis).

Side effects of unknown frequency (frequency cannot be estimated

from available data): - sudden circulatory failure caused by an acute allergic reaction (anaphylactic shock).

(anaphylactic shock).
 heart attack caused by an allergic reaction (Kounis syndrome).
 anemia with impaired function of the bone marrow (aplastic anemia), reduction in white and red blood cell and platelet counts (pancytopenia), including fatal cases. Signs of these changes in the blood include feeling generally unwell, infection, persistent fever, bruising, bleeding, and pallor.
 gastrointestinal bleeding.
 liver inflammation, vellowing of the skin and whites of the eves increase.

gastrointestinal bleeding.
liver inflammation, yellowing of the skin and whites of the eyes, increase in liver enzymes in the blood.
extensive rash, high temperature and enlarged lymph nodes (DRESS syndrome or drug hypersensitivity syndrome).
A harmless breakdown product of dipyrone may turn your urine red.

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.

You can report side effects to the Ministry of Health by following the link "Reporting Side Effects of Drug Treatment" on the Ministry of Health home page (<u>www.health.gov.il</u>) which links to an online form for reporting side effects. You can also use this link: <u>https://sideeffects.health.gov.il</u>

5. How to store the medicine?
 Prevent poisoning! To prevent poisoning, keep this and all other medicines in a closed place, out of the reach and sight of children and/

or infants. Do not induce vomiting unless explicitly instructed to do so

Do not use the medicine after the expiry date (exp. date) which is stated on the package. The expiry date refers to the last day of that month.
 Do not store above 25°C.

Use this medicine within 6 months of first opening the bottle, but no later than the expiry date listed on the package.

In addition to the active ingredient, the medicine also contains: Saccharin sodium, Raspberry aroma, Sodium Phosphate monobasic * $2H_2O$, Sodium Phosphate bibasic * 12 H₂O, Purified water.

Clear, colourless or slightly yellow liquid, with fruity taste and flavour. The bottle is made of yellow amber glass, with a dropper and a child safety cap. 20 ml package.

Raz Pharmaceuticals Ltd., 31 Gesher Haetz, Emek Hefer industrial park,

This leaflet was revised in March 2023 according to MOH guidelines. Registration number of the medicine in the Ministry of Health's

What the medicine looks like and contents of the pack:

Marketing authorization holder name and address:

National Drug Registry: 162-62-36039-00

RAZP4942-04

Dulergin PIL PB0223-05

Manufacturer name and address: A.B.C. Farmaceutici, Italy

Reporting side effects

6. Additional information

not use this medicine if"). - Reduction in the number of white blood cells (leucopenia). - Skin rash (such as maculopapular exanthema).

- to narcotic substances. Valproate, a medicine used to treat epilepsy or bipolar disorder. Tacrolimus, a medicine used to prevent organ rejection in patients with
- transplants Sertraline, a medicine used to treat depression.

Use of Pyrazolone drugs (the group of medicines to which Dulergin belongs) can interact with certain medicines: - medicines to prevent blood clotting. - captopril, a medicine for high blood pressure and certain heart disorders. - lithium, a medicine used to treat mental disorders. - diuretics such as triamferene. - medicines for lowering blood pressure. It is not known to what extent Dulergin causes these interactions between medicines

medicines

Effect on lab tests Tell your doctor that you are taking Dulergin before you have lab tests because the active ingredient dipyrone can affect the results of certain tests (for example, blood levels of creatinine, fats, HDL cholesterol, or uric acid). Take the medicine only after providing the blood sample for these tests.

Using Dulergin and alcohol It is advisable to avoid drinking any alcohol while taking Dulergin.

Using Dulergin and food It is best to take the drops with water. You can take Dulergin before or after a meal.

Pregnancy and breastfeeding If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, consult your doctor or pharmacist before taking this medicine.

Pregnancy The use during pregnancy can be done only after consulting a doctor, and only after the doctor has conducted a thorough risk-benefit assessment. In the third trimester (after week 28) you may use Dulergin only in the lowest

effective dose. After week 28: Do not take more than three grams (120 drops) a day, and for no more than 3-4 days in a row.

Breastfeeding The breakdown products of dipyrone pass into breast milk. While you are breastfeeding you may use Dulergin only if you do not respond to paracetamol or ibuprofen.

Driving and using machines This medicine is not known to affect the ability to concentrate and react when used within the recommended dosage range. However, as a precaution, at least at higher dosages, you should bear in mind that your ability to concentrate and react may be affected, so avoid using machines, driving, or other hazardous activities, particularly if you have been drinking alcohol.

Important information about some of this medicine's ingredients This medicine contains 38 mg of sodium (the main ingredient of table\cooking salt) in 1 ml (20 drops). This amount is equivalent to 1.9% of the recommended maximum daily intake of sodium for an adult.

Ethanol: This medicine contains 6 mg of alcohol (ethanol) in 1 ml (20 drops). This amount is equivalent to less than 1 ml of beer or 1 ml of wine.

3. <u>How to use this medicine?</u> Check with your doctor or pharmacist if you are not sure about your dose or about how to take this medicine. Your dose will be determined based on the severity of the pain or fever and depending on your individual response to Dulergin. Dose can be determined by the patient's age or weight. Take the lowest effective dose.

In the absence of other directions from your doctor, the recommended dose is Take the correct dose as shown in the table below. Take the medicine at

- Take the control duse as shown in the basis of the state intervals of 6-8 hours. It is advisable to dose children by weight according to the table. You may determine the dose by the child's age, only if you do not know the child's
- Do not take more than three doses in 24 hours. These drops are not intended for babies weighing less than 5 kg.

Adults and adolescents over 15 years old (weighing over 53 kg):

20-40 drops, up to 3 times a day

Babies and children:

Age	Body weight (kg)	Dose (number of drops)
3-11 months	5-8	2-4 drops, up to 3 times a day
1-3 years	9-15	3-10 drops, up to 3 times a day
4-6 years	16-23	5-15 drops, up to 3 times a day
7-9 years	24-30	8-20 drops, up to 3 times a day
10-12 years	31-45	10-30 drops, up to 3 times a day
13-14 years	46-53	15-35 drops, up to 3 times a day

Consult your doctor if your fever lasts more than 3 days or pain persists for more than 7 days, even though you are using the medicine. There is a greater risk of agranulocytosis if treatment continues for longer than 7 days (see the section 4 - "Side effects").

Elderly patients, patients in poor general health, or patients with impaired

kidney function Reduce the dose because the elimination of Dulergin breakdown products may be slowed down.

Patients with impaired kidney or liver function Repeated high doses should be avoided, as the elimination rate is reduced when kidney or liver function is impaired. It is not necessary to reduce the dose if only used for a short time. There is no experience with long-term use. Do not exceed the recommended dose.

How to use the medicine

4. Side effects

These drops are for oral administration only. It is best to take the drops with water. You can take this medicine before or after a meal. Make sure the cap is closed securely after using.

If you have accidentally taken an overdose, or if a child has accidentally swallowed some medicine, immediately see a doctor or go to a hospital emergency room and bring the medicine package with you. Signs of overdose include:

nausea, vomiting, abdominal pain, reduced kidney function to the extent of acute kidney failure, dizziness, drowsiness, loss of consciousness, convulsions, sharp drop in blood pressure to the extent of circulatory failure, fast heart rhythm. If you suspect an overdose, tell your doctor immediately so suitable measures can be applied.

Note: After very high doses of this medicine, excretion of a harmless breakdown roduct of dipyrone may turn your urine red.

If you forget to take the medicine, do not take a double dose to make up for the forgotten dose Do not take medicines in the dark! Check the label and dose every time you

If you have any further questions about using this medicine, consult your doctor or pharmacist.

A: Stude effects Like with all medicines, using Dulergin may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them.

The following side effects may have serious consequences; stop taking

or pancytopenia) may sometimes be life-threatening. In such cases, you must