**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 ingredients" 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 questions, 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.
**This medicine is given without need for a prescription. 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:** The active ingredient belongs to the pyrazolone group.

## 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 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 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).
· 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-

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 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".
- 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 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 DULERGIN or other reactions mediated by the immune system (such 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 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.

**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).
- 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**
There have been reports of life-threatening skin reactions (Stevens- Johnson syndrome, toxic epidermal necrolysis) following use of dipyrone. Stop treatment with DULERGIN immediately if you develop a skin rash, often associated with blisters or damage to mucous membranes. Never take dipyrone 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 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:
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. 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**
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.
- Chlorpromazine, a medicine used to treat mental disorders - Using DULERGIN at the same time may cause a serious fall in your body temperature.
- Efavirenz, a medicine used to treat HIV/AIDS.
- Methadone, a medicine used to treat severe pain or withdrawal from addiction 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.

Pyrazolones (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 triamterene
- medicines for lowering blood pressure

It is not known to what extent DULERGIN causes these interactions between 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). If you have to give a blood sample for any of these tests, take the medicine only after the blood sample has been collected.

**Using this medicine 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

Only use during pregnancy after consulting your doctor, and only after your 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**
One mg of this medicine contains 38 mg sodium (the main ingredient of table 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 about 6 mg alcohol (ethanol) in 20 drops. This amount is equivalent to less than 1 ml beer or wine.

## 3. How to use this medicine?

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 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 weight.
- Do not take a dose more than 3 times 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**
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, cramps, 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 product 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 missed dose.

**Do not take medicines in the dark! Check the label and dose every time you take medicine. Wear glasses if you need them.**
**If you have any further questions about using this medicine, consult your doctor or pharmacist.**

## 4. Side 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 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 or toxic epidermal necrolysis; agranulocytosis or pancytopenia) may sometimes be life-threatening. In such cases, you must 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 under "Special warnings about using this medicine"), 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 available.
- If you get the following symptoms, which could be signs of liver damage (see also section 2 under "Special warnings about using this medicine"): 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.

**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. The risk of a 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 abdominal 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").
- Reduction in the number of white blood cells (**leucopenia**).
- **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 thrombocytopenia include an increased bleeding tendency and red pinpoint spots on the skin and mucous membranes caused by bleeding.

- **Asthma attack**
- Extensive blistering 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).
- **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, yellowing of the skin and whites of the eyes, increase in liver enzymes in the blood.

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.**

**Reporting side effects**
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 (www.health.gov.il) which links to an online form for reporting side effects. You can also use this link:
https://sideeffects.health.gov.il

## 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 by a doctor.
- 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.
- **Store below 25°C.**
- **Use this medicine within 6 months of first opening the bottle, but no later than the expiry date listed on the package.**

## 6. Additional information

**In addition to the active ingredient, the medicine also contains:** Sodium Phosphate monobasic

* $2H_2O$ , Sodium Phosphate bibasic * 12 $H_2O$, Raspberry aroma, Saccharin sodium, Purified water.

## What the medicine looks like and contents of the pack:

Clear liquid, either colorless or light yellow in color, with the flavor and scent of fruit. The vial is made of amber glass, with a dropper and a child safety cap. 20 ml package.

## Marketing authorization holder name and address:

Raz Pharmaceuticals Ltd., 6 Hamatechet St., Kadima**.**

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

This leaflet was revised in December 2021 according to MOH guidelines.

Registration number of the medicine in the Ministry of Health's National Drug Registry: 162-62-36039-00.

RAZP4942-02