

PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS - 1986

This medicine is dispensed with a physician's prescription only

Orfadin™ 2 mg Hard capsules

Orfadin™ 5 mg Hard capsules

Orfadin™ 10 mg Hard capsules

Composition:

Active ingredient:

Each capsule of ORFADIN 2 MG HARD CAPSULES contains Nitisinone 2 mg

Each capsule of ORFADIN 5 MG HARD CAPSULES contains Nitisinone 5 mg

Each capsule of ORFADIN 10 MG HARD CAPSULES contains Nitisinone 10 mg

For the list of inactive ingredients and allergens in the medicine, see section 6, "Additional information".

Read this leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, consult your physician or pharmacist.

This medicine has been prescribed to treat your illness. Do not pass it on to others. It may harm them even if it seems to you that their illness is similar.

1. What is this medicine intended for?

Treatment of patients with confirmed diagnosis of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine.

In this disease your body is unable to completely break down the amino acid tyrosine (amino acids are the building blocks that build the proteins in our body), and as a result, a harmful substance accumulates in the body. **Orfadin hard capsules** prevent the breakdown of the amino acid tyrosine from the outset, and as a result, the harmful substance does not accumulate in your body.

Since tyrosine remains in the body, a special dietary regime based on foods with low quantities of tyrosine and phenylalanine should be maintained during treatment with **Orfadin hard capsules**.

Therapeutic group: Treatment of defects in an essential metabolic system.

2. Before using the medicine:

Do not use this medicine if:

- You are sensitive (allergic) to the active ingredient nitisinone or to any of the additional ingredients that the medicine contains (please see section 6, "Additional information").
- Do not breastfeed while taking this medicine.

Special warnings regarding the use of the medicine Before and during treatment with Orfadin hard capsules, tell your physician:

- If redness or any other sign appears in your eyes, consult

a physician immediately for an eye examination. Eye problems could indicate inadequate dietary control.

Tests and follow-up:

Before and during treatment with this medicine, have your eyes examined by an ophthalmologist.

During the treatment period, you will be referred for blood tests to check whether the treatment is effective and to make sure that there are no side effects causing blood disorders.

Periodically, liver tests should be performed because the disease tyrosinemia type 1 affects the liver.

You should see your physician for a follow-up examination every six months, and more frequently if side effects occur.

Drug interactions:

If you are taking or have recently taken other medicines, including non-prescription medicines and nutritional supplements, tell your physician or pharmacist.

Orfadin hard capsules may interfere with the effect of other medicines, such as:

- Medicines for epilepsy, such as phenytoin
- Medicines against blood clotting, such as coumadin / warfarin

Use of the medicine and food:

If you start treatment with **Orfadin hard capsules** by taking it with food, it is recommended that you carry on taking **Orfadin hard capsules** with food throughout the treatment.

Pregnancy, breastfeeding and fertility:

The safety of **Orfadin hard capsules** has not been studied in pregnant or breastfeeding women. Inform your physician if you are planning to become pregnant. If you are pregnant, inform your physician immediately.

Do not breastfeed while taking this medicine.

Driving and operating machinery:

During the use of this medicine, there may be a minor effect that could impair alertness, thus necessitating caution when driving a vehicle, operating dangerous machinery, and during any activity that requires alertness.

There may be an effect on vision that could appear during the treatment. If you experience this, avoid driving or operating dangerous machinery until your vision is back to normal.

3. How should you use the medicine?

Always use this medicine according to your physician's instructions. If you are not sure about the dosage or treatment regimen, consult your physician or pharmacist.

Initiation of treatment with **Orfadin hard capsules** should be under the instructions and supervision of a physician experienced in the treatment of patients with hereditary tyrosinemia type 1.

The usual dosage is generally: 1 mg for each kilogram of your weight per day. Your physician will adjust your dose individually.

It is desirable to administer the dose once daily.

However, due to the limited data in patients with body weight less than 20 kilograms, it is recommended that these patients divide the dose to twice a day.

If you have swallowing problems, the capsule may be opened and the powder mixed with a small amount of water or nutritional formula just before taking the medicine.

Do not exceed the recommended dose.

If you accidentally took a higher dosage or if a child has accidentally swallowed the medicine, proceed immediately to a physician or a hospital emergency room and bring the package of the medicine with you.

If you forgot to take the medicine at the required time, do not take a double dose. Take the next dose at the regular time and consult your physician.

Adhere to the treatment regimen as recommended by your physician.

Do not stop taking the medicine or change the dosage without consulting your physician, even if it seems to you that the medicine is not working properly.

Do not take medicines in the dark! Check the label and the dose each time you take a medicine. Wear glasses if you need them.

If you have further questions regarding use of the medicine, consult your physician or pharmacist.

4. Side effects:

As with any medicine, the use of **Orfadin hard capsules** may cause side effects in some users. Do not be alarmed by the list of side effects. You may not experience any of them.

If you notice side effects related to the eyes, talk to your physician immediately to have an eye examination. Treatment with nitisinone leads to high levels of tyrosine in the blood, which can cause eye-related symptoms. The following effects are caused by higher levels of tyrosine:

Common side effects (effects that occur in 1-10 in 100 users):

- Inflammation of the eye (conjunctivitis)
- Opacity and inflammation of the cornea (keratitis)
- Sensitivity to light (photophobia) and eye pain

Uncommon side effects (effects that occur in 1-10 in 1,000 users):

- Inflammation of the eyelid (blepharitis)

Additional side effects:

Common side effects (effects that occur in 1-10 in 100 users):

- Reduced level of platelets (thrombocytopenia) and white blood cells (leukopenia), deficiency of a certain type of white blood cells (granulocytopenia)

Uncommon side effects (effects that occur in 1-10 in 1,000 users):

- Increased number of white blood cells (leucocytosis)
- Itching (pruritus), skin inflammation (exfoliative dermatitis) and rash

If a side effect occurs, if one of the side effects worsens or if you suffer from a side effect not mentioned in this leaflet, consult your physician.

Side effects can be reported to the Ministry of Health by clicking on the link "Report on Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link:

<https://sideeffects.health.gov.il>.

5. How should the medicine be stored?

- Avoid poisoning! This medicine and any other medicine should be kept in a closed place out of the reach and

sight of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by your physician.

• Do not use this medicine after the expiry date (exp. Date) which appears on the outer package. The expiry date refers to the last day of that month.

• Do not throw away medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

Storage conditions

- Store in the refrigerator (2-8°C).

• Orfadin 2 mg hard capsules:

- The capsules may be stored outside the refrigerator at a temperature that does not exceed 25 degrees Celsius for a period of up to 2 months. After this period, the package should be discarded.
- Use within 2 months of first opening.

• Orfadin 5 mg hard capsules:

- The capsules may be stored outside the refrigerator at a temperature that does not exceed 25 degrees Celsius for a period of up to 3 months. After this period, the package should be discarded.
- Use within 2 months of first opening.

• Orfadin 10 mg hard capsules:

- The capsules may be stored outside the refrigerator at a temperature that does not exceed 25 degrees Celsius for a period of up to 3 months. After this period, the package should be discarded.
- Use within 2 months of first opening.

6. Additional information:

• In addition to the active ingredient nitisinone, this medicine also contains:

starch pregelatinise, gelatine, titanium dioxide, black iron oxide (E172)

• What the medicine looks like and the contents of the package:

White opaque hard capsules imprinted in black with "NTBC" on one side, and on the other side with the strength of the medicine: 2 mg/ 5 mg/ 10 mg. The capsule contains a white to off-white powder.

• **Orfadin hard capsules** are marketed in packages of 60 capsules in plastic bottles with a child resistant cap.

• Registration holder and address:

Megapharm Ltd., P.O.B. 519, Hod Hasharon 4510501, Israel.

• Manufacturer and address:

Apotek Produktion & Laboratorier, Kungens Kurva, Sweden, for Swedish Orphan Biovitrum International (SOBI), Stockholm, Sweden.

• Revised on January 2020

• Registration number of the medicine in the National Drug Registry of the Ministry of Health:

Orfadin 2 mg hard capsules - 147-25-33445

Orfadin 5 mg hard capsules - 147-26-33456

Orfadin 10 mg hard capsules - 147-27-33457