Package leaflet: Information for the user

Orfadin 4 mg/ml oral suspension
nitisinone

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Orfadin is and what it is used for
2. What you need to know before you take Orfadin
3. How to take Orfadin
4. Possible side effects
5. How to store Orfadin
6. Contents of the pack and other information

1. What Orfadin is and what it is used for

Orfadin contains the active substance nitisinone. Orfadin is used to treat:
- a rare disease called hereditary tyrosinemia type 1 in adults, adolescents and children (in any age range)
- a rare disease called alkaptonuria (AKU) in adults.

In these diseases your body is unable to completely break down the amino acid tyrosine (amino acids are building blocks of our proteins), forming harmful substances. These substances are accumulated in your body. Orfadin blocks the breakdown of tyrosine and the harmful substances are not formed.

For the treatment of hereditary tyrosinemia type 1, you must follow a special diet while you are taking this medicine, because tyrosine will remain in your body. This special diet is based on low tyrosine and phenylalanine (another amino acid) content.

For the treatment of AKU, your doctor may advise you to follow a special diet.

2. What you need to know before you take Orfadin

Do not take Orfadin
- if you are allergic to nitisinone or any of the other ingredients of this medicine (listed in section 6).

Do not breast-feed while taking this medicine, see section “Pregnancy and breast-feeding”.

Warnings and precautions
Talk to your doctor or pharmacist before taking Orfadin.
- Your eyes will be checked by an ophthalmologist before and regularly during nitisinone treatment. If you get red eyes or any other signs of effects on the eyes, contact your doctor immediately for an eye examination. Eye problems could be a sign of inadequate dietary control (see section 4).

During the treatment, blood samples will be drawn in order for your doctor to check whether the treatment is adequate and to make sure that there are no possible side effects causing blood disorders.

If you receive Orfadin for treatment of hereditary tyrosinemia type 1, your liver will be checked at regular intervals because the disease affects the liver.

Follow-up by your doctor should be performed every 6 months. If you experience any side effects, shorter intervals are recommended.

Other medicines and Orfadin
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
Orfadin may interfere with the effect of other medicines, such as:
- Medicines for epilepsy (such as phenytoin)
- Medicines against blood clotting (such as warfarin).

Orfadin with food
It is recommended that the oral suspension is taken with food.

Pregnancy and breast-feeding
The safety of this medicine has not been studied in pregnant and breast-feeding women.
Please contact your doctor if you plan to become pregnant. If you become pregnant you should contact your doctor immediately.
Do not breast-feed while taking this medicine, see section “Do not take Orfadin”.

Driving and using machines
This medicine has minor influence on the ability to drive and use machines. However, if you experience side effects affecting your vision you should not drive or use machines until your vision is back to normal (see section 4 “Possible side effects”).

Orfadin contains sodium, glycerol and sodium benzoate
This medicinal product contains 0.7 mg (0.03 mmol) sodium per ml.
A dose of 20 ml oral suspension (10 g glycerol) or more may cause headache, stomach upset and diarrhoea.
Sodium benzoate may increase jaundice (yellowing of the skin and eyes) in pre-term and full-term jaundiced neonates and develop into kernicterus (brain damage due to deposits of bilirubin in the brain). The newborn baby’s blood levels of bilirubin (a substance that causes the yellowing of the skin in high levels) will be closely monitored. If the levels are markedly higher than they should be, especially in premature babies with risk factors as acidosis (too low pH in the blood) and low albumin level (a protein in the blood) treatment with Orfadin capsules will be considered instead of the oral suspension until the bilirubin plasma levels are normalised.

3. How to take Orfadin

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Follow the instructions given below for dose preparation and administration carefully, in order to ensure that the correct dose is administered.

For hereditary tyrosinemia type 1, treatment with this medicine should be started and supervised by a doctor experienced in the treatment of the disease.

For hereditary tyrosinemia type 1, the recommended total daily dose is 1 mg/kg body weight administered orally. Your doctor will adjust the dose individually.
It is recommended to administer the dose once daily. However, due to the limited data in patients with body weight <20 kg, it is recommended to divide the total daily dose into two daily administrations in this patient population.

For AKU, the recommended dose is 10 mg once daily.

The oral suspension is taken with a oral syringe directly in the mouth without dilution.
Orfadin must not be injected. Do not attach a needle to the syringe.

How to prepare the dose to be administered
The dose that your doctor prescribes you should be given in **ml of suspension** and not in mg. This is because the oral syringe which is used to withdraw the correct dose from the bottle is marked in ml. **If your prescription is in mg, contact your pharmacist or doctor for advice.**

The pack contains a bottle of medicine with a cap, a bottle adaptor and three oral syringes (1.5 ml, 3 ml and 6 ml). Always use one of the oral syringes provided to take the medicine.

- The 1.5-ml oral syringe (the smallest oral syringe) is marked from 0.1 ml to 1.5 ml with minor 0.05-ml graduations. It is used for measuring doses of less than or up to 1.5 ml.
- The 3 ml oral syringe (the middle sized oral syringe) is marked from 1 ml to 3 ml with minor 0.1-ml graduations. It is used for measuring doses of more than 1.5 ml and up to 3 ml.
- The 6 ml oral syringe (the largest oral syringe) is marked from 1 ml to 6 ml with minor 0.25-ml graduations. It is used for measuring doses of more than 3 ml.

It is important that you use the correct oral syringe when taking the medicine. Your doctor, pharmacist or nurse will advise which oral syringe to use depending on the dose that has been prescribed.

<u>How to prepare a new bottle of medicine for first time use:</u>

Before you take the first dose, shake the bottle vigorously since during long-term storage the particles will form a solid cake at the bottom of the bottle. Follow the instructions below:

Figure A

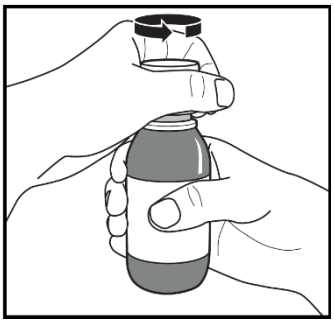
Figure B

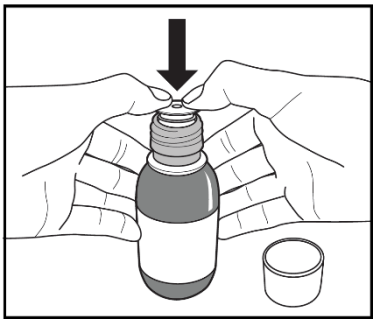
Figure C

1. Remove the bottle from the refrigerator. Note the date when the bottle is removed from the refrigerator on the bottle label.
2. Shake the bottle vigorously for **at least 20 seconds** until the solid cake at the bottom of the bottle is completely dispersed (Figure A).
3. Remove the child resistant screw cap by pushing it down firmly and turning it anti-clockwise (Figure B).
4. Place the open bottle upright on a table. Push the plastic adapter firmly into the neck of the bottle as far as you can (Figure C) and close the bottle with the child resistant screw cap.

For subsequent dosing see the instructions below ‘How to prepare a dose of medicine’.

How to prepare a dose of medicine

Figure D

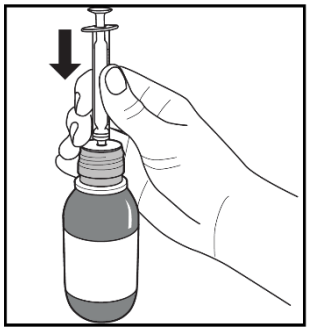

Figure E

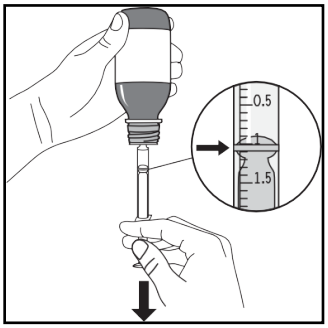

Figure F

1. Shake the bottle vigorously for **at least 5 seconds** (Figure D).
2. Immediately thereafter, open the bottle by removing the child resistant screw cap.
3. Push the plunger inside the oral syringe fully down.
4. Keep the bottle in an upright position and insert the oral syringe firmly into the hole at the top of the bottle (Figure E).
5. Carefully turn the bottle upside down with the oral syringe in place (Figure F).
6. In order to withdraw the prescribed dose (ml), pull the plunger **slowly** down until the top edge of the plunger is exactly level with the line marking the dose (Figure F). If any air bubbles are observed inside the filled oral syringe, push the plunger back up until the air bubbles are expelled. Then pull the plunger down again until the top edge is exactly level with the line marking the dose.
7. Turn the bottle to an upright position again. Disconnect the oral syringe by gently twisting it out of the bottle.
8. The dose should be administered in the mouth immediately (without dilution) in order to avoid caking in the oral syringe. The oral syringe must be emptied **slowly** to allow swallowing; rapid squirting of the medicine may cause choking.
9. Replace the child resistant screw cap directly after use. The bottle adapter should not be removed.
10. The bottle may be stored at room temperature (not above 25°C).

Cleaning:
Clean the oral syringe **immediately** with cold tap water only, and if necessary, move the plunger in and out. Shake off excess water and leave the oral syringe to dry until the next dosing occasion. Do not disassemble the oral syringe.

If you take more Orfadin than you should
If you have taken more of this medicine than you should, contact your doctor or pharmacist as soon as possible.

If you forget to take Orfadin
Do not take a double dose to make up for a forgotten dose. If you forget to take a dose, contact your doctor or pharmacist.

If you stop taking Orfadin
If you have the impression that the medicine is not working properly, talk to your doctor. Do not change the dose or stop the treatment without talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you notice any side effects relating to the eyes, talk to your doctor immediately to have an eye examination. Treatment with nitisinone leads to higher levels of tyrosine in the blood which can cause eye related symptoms. In patients with hereditary tyrosinemia type 1, commonly reported eye related side effects (may affect more than 1 in 100 people) caused by higher tyrosine levels are inflammation in the eye (conjunctivitis), opacity and inflammation in the cornea (keratitis), sensitivity to light (photophobia) and eye pain. Inflammation of the eyelid (blepharitis) is an uncommon side effect (may affect up to 1 in 100 people).
In AKU patients, eye irritation (keratopathy) and eye pain are very commonly reported side effects (may affect more than 1 in 10 people).

Other side effects reported in patients with hereditary tyrosinemia type 1 are listed below:

Other common side effects
- reduced number of platelets (thrombocytopenia) and white blood cells (leukopenia), shortage of certain white blood cells (granulocytopenia).

Other uncommon side effects
- increased number of white blood cells (leucocytosis),
- itching (pruritus), skin inflammation (exfoliative dermatitis), rash.

Other side effects reported in patients with AKU are listed below:

Other common side effects
- bronchitis
- pneumonia
- itching (pruritus), rash.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via:

Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard
or search for MHRA Yellow Card in the Google Play or Apple App Store

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Orfadin

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle and carton after “EXP”. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store the bottle upright.

After first opening, the medicine can be stored for a single period of 2 months at a temperature not above 25°C, after which it must be discarded.

Do not forget to mark the date on the bottle, when removed from the refrigerator.

Do not throw away any 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.

6. Contents of the pack and other information

What Orfadin contains
- The active substance is nitisinone. Each ml contains 4 mg nitisinone.
- The other ingredients are hydroxypropylmethylcellulose, glycerol (see section 2), polysorbate 80, sodium benzoate (E211) (see section 2), citric acid monohydrate, sodium citrate (see section 2), strawberry aroma (artificial) and purified water.

What Orfadin looks like and contents of the pack
The oral suspension is a white, slightly thicker opaque suspension. Before shaking the bottle, it may look like a solid cake in the bottom and a slightly opalescent liquid. It is provided in a 100 ml brown glass bottle with a white, child resistant screw cap. Each bottle contains 90 ml supension.
Each pack contains one bottle, one bottle adapter and three oral syringes.

Marketing Authorisation Holder
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Apotek Produktion & Laboratorier AB
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SE-212 14 Malmö
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