PACKAGE LEAFLET

Package leaflet: Information for the patient

Onpattro 2 mg/mL concentrate for solution for infusion
patisiran

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given 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 or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Onpattro is and what it is used for

The active substance in Onpattro is patisiran.

Onpattro is a medicine that treats an illness which runs in families called hereditary ATTR (hATTR) amyloidosis.

hATTR amyloidosis is caused by problems with a protein in the body called ‘transthyretin’ (TTR).
- This protein is made mostly in the liver and carries vitamin A and other substances around the body.
- In people with this illness, abnormally shaped TTR proteins clump together to make deposits called ‘amyloid’.
- Amyloid can build up around the nerves, heart, and other places in the body, preventing them from working normally. This causes the symptoms of the illness.

Onpattro works by lowering the amount of TTR protein that the liver makes.
- This means there is less TTR protein in the blood that can form amyloid.
- This can help to reduce the effects of this illness.

Onpattro is used in adults only.

2. What you need to know before you are given Onpattro

You must not be given Onpattro
- if you have ever had a severe allergic reaction to patisiran, or any of the other ingredients of this medicine (listed in section 6). If you are not sure, talk to your doctor or nurse before you are given Onpattro.

Warnings and precautions

Infusion-related reactions

Onpattro is given as a drip into a vein (called an 'intravenous infusion'). Reactions to this infusion may happen during treatment with Onpattro. Before each infusion you will be given medicines that help to lower the chance of infusion-related reactions (see "Medicines given during treatment with Onpattro" in section 3).

Tell your doctor or nurse straight away if you get any signs of an infusion-related reaction. These signs are listed at the beginning of section 4.

If you have an infusion-related reaction, your doctor or nurse may slow down or stop your infusion, and you may need to take other medicines to control the symptoms. When these reactions stop, or get better, your doctor or nurse may decide to start the infusion again.

Vitamin A deficiency

Treatment with Onpattro lowers the amount of vitamin A in your blood. Your doctor will measure your vitamin A levels, and if they are too low they should have returned to normal and any symptoms due to vitamin A deficiency should have resolved before you start treatment with Onpattro. Symptoms of vitamin A deficiency may include:

- Decrease in night vision, dry eyes, poor vision, hazy or cloudy vision

If you have problems with your vision or any other eye problems whilst using Onpattro, you should talk to your doctor. Your doctor may refer you to an eye specialist for a check-up if it is necessary.

Your doctor will ask you to take a daily vitamin A supplement during treatment with Onpattro.

Both too high and too low levels of vitamin A can harm the development of your unborn child. Therefore, women of child-bearing age should not be pregnant when starting treatment with Onpattro and should practice effective contraception (see section "Pregnancy, breast-feeding and contraception" below).

Tell your doctor if you are planning to become pregnant. Your doctor may tell you to stop taking Onpattro. Your doctor will ensure that your vitamin A levels have returned to normal before you try to become pregnant.

Tell your doctor if you have an unplanned pregnancy. Your doctor may tell you to stop taking Onpattro. During the first 3 months of your pregnancy, your doctor may tell you to stop your vitamin A supplement. During the last 6 months of your pregnancy you should resume vitamin A supplementation if the vitamin A levels in your blood have not yet returned to normal, because of an increased risk of vitamin A deficiency during the last 3 months of your pregnancy.

Children and adolescents
Onpattro is not recommended in children and adolescents under 18 years of age.

Other medicines and Onpattro
Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines. It is important to tell your doctor or nurse if you are taking any of the following medicines as your doctor may need to change the dose:

- Bupropion, a medicine used to treat depression or to help you to stop smoking
- Efavirenz, a medicine used to treat HIV infection and AIDS

Pregnancy, breast-feeding and contraception
If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before starting this medicine.

Women of child-bearing age

Onpattro will reduce the level of vitamin A in your blood, which is important for normal development of your unborn child. If you are a woman of child-bearing age, you should practice effective contraception during treatment with Onpattro. Talk to your doctor or nurse about suitable methods of contraception. Pregnancy should be excluded before starting treatment with Onpattro.

Pregnancy

You should not use Onpattro if you are pregnant, unless advised by your doctor. If you are of child-bearing age and intend to use Onpattro, you should practise effective contraception.

Breast-feeding

Ingredients of Onpattro may pass into breast milk. Talk to your doctor about stopping breast-feeding or treatment with Onpattro.

Driving and using machines
Onpattro is believed to have no or negligible influence on the ability to drive or use machines. Your doctor will tell you whether your condition allows you to drive vehicles and use machines safely.

Onpattro contains sodium
This medicine contains 3.99 milligrams (mg) of sodium (main component of cooking/table salt) per millilitre (mL). This is 0.2% of the recommended maximum daily dietary intake of sodium for an adult.

3. How Onpattro is given

How much Onpattro is given
- Your doctor will work out how much Onpattro to give you – this will depend on your body weight.
- The usual dose of Onpattro is 300 micrograms per kilogram (kg) of body weight given once every 3 weeks.

How Onpattro is given
- Onpattro will be given to you by a doctor or nurse.
- It is given as a drip into a vein (‘intravenous infusion’) usually over about 80 minutes.

If you do not have problems with your infusions in the clinic, your doctor may talk with you about a healthcare professional giving you your infusions at home.

Medicines given during treatment with Onpattro
Before each infusion of Onpattro, you will be given medicines that help to lower the risk of infusion-related reactions. These include anti-histamines, a corticosteroid (a medicine that suppresses inflammation), and a pain reliever.

How long to use Onpattro
Your doctor will tell you how long you need to receive Onpattro. Do not stop treatment with Onpattro unless your doctor tells you to.

If you are given more Onpattro than you should receive
This medicine will be given to you by your doctor or nurse. In the unlikely event that you are given too much (an overdose) your doctor or nurse will check you for side effects.

If you miss your dose of Onpattro
If you miss an appointment to have Onpattro, ask your doctor or nurse when to book your next treatment.

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

4. Possible side effects

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

Infusion-related reactions
Infusion-related reactions are very common (may affect more than 1 in 10 people).

Tell your doctor or nurse straight away if you get any of the following signs of an infusion-related reaction during treatment. The infusion may need to be slowed down or stopped, and you may need to take other medicines to manage the reaction.
- Stomach pain
- Feeling sick (nausea)
- Body aches or pain, including pain in the back, neck, or joints
- Headache
- Feeling tired (fatigue)
- Chills
- Dizziness
- Cough, feeling short of breath, or other breathing problems
- Reddening of the face or body (flushing), warm skin, rash or itching
- Chest discomfort or chest pain
- Rapid heart rate
- Low or high blood pressure; some patients have fainted during the infusion due to low blood pressure
- Pain, redness, burning sensation, or swelling at or near the infusion site
- Swelling of the face

Other side effects
Tell your doctor or nurse if you notice any of the following side effects:

Very common: may affect more than 1 in 10 people
- Swelling of the arms or legs (peripheral oedema)

Common: may affect up to 1 in 10 people
- Pain in the joints (arthralgia)
- Muscle spasms
- Indigestion (dyspepsia)
- Shortness of breath (dyspnoea)
- Redness of the skin (erythema)
- Feeling dizzy or faint (vertigo)
- Stuffy or runny nose (rhinitis)
- Irritation or infection of the airways (sinusitis, bronchitis)

Uncommon: may occur in up to 1 in 100 infusions
- Leakage of the drug into the surrounding tissue at the site of infusion, which may cause swelling or redness

Tell your doctor or nurse if you notice any of the side effects listed above.

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

United Kingdom
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 Onpattro

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 carton after 'EXP'. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C). Do not freeze.

If refrigeration is not available, Onpattro can be stored at room temperature (up to 25°C) for up to 14 days.

Medicines should not be disposed of via wastewater or household waste. Your healthcare professional will throw away any medicines that are no longer being used. These measures will help protect the environment.

6. Contents of the pack and other information

What Onpattro contains
- The active substance is patisiran.
- Each mL contains patisiran sodium equivalent to 2 mg patisiran.
- Each 5 mL vial contains patisiran sodium equivalent to 10 mg patisiran.
- The other ingredients are DLin-MC3-DMA ((6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4- (dimethylamino) butanoate), PEG_{2000}-C-DMG (α- (3'-{[1,2-di(myristyloxy)propanoxy]carbonylamino}propyl)-ω-methoxy, polyoxyethylene), DSPC (1,2-distearoyl-*sn*-glycero-3-phosphocholine), cholesterol, disodium hydrogen phosphate, heptahydrate, potassium dihydrogen phosphate, anhydrous, sodium chloride, and water for injections (see "Onpattro contains sodium" in section 2).

What Onpattro looks like and contents of the pack
- Onpattro is a white to off-white, opalescent, homogeneous concentrate for solution for infusion.
- Onpattro is supplied in cartons containing one vial each.

Marketing Authorisation Holder and Manufacturer
Alnylam Netherlands B.V.
Antonio Vivaldistraat 150
1083 HP Amsterdam
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder

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The following information is intended for healthcare professionals only:

Required premedication

All patients should receive premedication prior to Onpattro administration to reduce the risk of infusion-related reactions (IRRs). Each of the following medicinal products should be given on the day of Onpattro infusion at least 60 minutes prior to the start of infusion:

- Intravenous corticosteroid (dexamethasone 10 mg, or equivalent)
- Oral paracetamol (500 mg)
- Intravenous H1 blocker (diphenhydramine 50 mg, or equivalent)
- Intravenous H2 blocker (ranitidine 50 mg, or equivalent)

For premedications not available or not tolerated intravenously, equivalents may be administered orally.

If clinically indicated, the corticosteroid may be tapered in decrements no greater than 2.5 mg to a minimum dose of 5 mg of dexamethasone (intravenous, IV), or equivalent. The patient should receive at least 3 consecutive infusions of Onpattro without experiencing IRRs before each reduction in corticosteroid premedication.

Additional or higher doses of one or more of the premedications may be administered to reduce the risk of IRRs, if needed.

Preparation of the solution for infusion

This medicinal product is for single-use only.

Onpattro must be diluted with sodium chloride 9 mg/mL (0.9%) solution prior to intravenous infusion. The diluted solution for infusion should be prepared by a healthcare professional using aseptic technique as follows:

- Remove Onpattro from the refrigerator. Do not shake or vortex.
- Discard vial if it has been frozen.
- Inspect visually for particulate matter and discolouration. Do not use if discolouration or foreign particles are present. Onpattro is a white to off-white, opalescent, homogeneous solution. A white to off-white coating may be observed on the inner surface of the vial, typically at the liquid-headspace interface. Product quality is not impacted by presence of the white to off-white coating.
- Calculate the required volume of Onpattro based on the recommended weight-based dosage.
- Withdraw the entire contents of one or more vials into a single sterile syringe.
- Filter Onpattro through a sterile 0.45 micron polyethersulfone (PES) syringe filter into a sterile container.

- Withdraw the required volume of filtered Onpattro from the sterile container using a sterile syringe.
- Dilute the required volume of filtered Onpattro into an infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for a total volume of 200 mL. Use infusion bags that are free of di(2-ethylhexyl)phthalate (DEHP).
- Gently invert the bag to mix the solution. Do not shake. Do not mix or dilute with other medicinal products.
- Discard any unused portion of Onpattro. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
- Onpattro does not contain preservatives. The diluted solution should be administered immediately after preparation. If not used immediately, store the diluted solution in the infusion bag at room temperature (up to 30°C) or at 2°C to 8°C for up to 16 hours (including infusion time). Do not freeze.

Administration

Onpattro is for intravenous use.
- Onpattro must be diluted prior to intravenous infusion.
- A dedicated line with an infusion set containing a 1.2 micron PES in-line infusion filter must be used. The infusion sets must be free of di(2-ethylhexyl) phthalate (DEHP).
- The diluted solution of Onpattro should be infused intravenously over approximately 80 minutes at an initial infusion rate of approximately 1 mL/min for the first 15 minutes, followed by an increase to approximately 3 mL/min for the remainder of the infusion. The duration of infusion may be extended in the event of an IRR.
- Onpattro must be administered through a secure and free-flowing venous access line. The infusion site should be monitored for possible infiltration during administration. Suspected extravasation should be managed according to local standard practice for non-vesicants.
- The patient should be observed during the infusion and, if clinically indicated, following the infusion.
- After completion of the infusion, the intravenous administration set should be flushed with sodium chloride 9 mg/mL (0.9%) solution to ensure that all medicinal product has been administered.