

Early Access to Medicines Scientific Opinion - Public Assessment Report Patisiran-LNP

Patisiran-LNP is indicated for the treatment of adults with hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis).

Alnylam UK Limited

EAMS 43942/0001

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed medicines to UK patients that have a high unmet clinical need. The MHRA scientific opinion provides benefit and risk information to doctors who may wish to prescribe the unlicensed medicine under their own responsibility. More information about the scheme can be found here: <http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm>

The scientific opinion is based on the information supplied to the MHRA on the benefits and risks of a promising new medicine. As such this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to licence such a medicine. The General Medical Council's guidance on prescribing unlicensed medicines can be found here: https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

What is patisiran-LNP?

Patisiran-LNP is a medicine that contains a substance called patisiran in a solution for infusion into a vein. Patisiran is a large molecule that reduces the levels of a protein mainly produced in the liver that may deposit in nerves, heart and the gastrointestinal tract if its production is abnormal.

What is patisiran-LNP used to treat?

Patisiran-LNP 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 other substances around the body - such as vitamin A.
- In people with this illness, TTR proteins can misfold (take on an abnormal shape). These misfolded proteins can gather 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 this illness.

How is patisiran-LNP used?

Treatment with patisiran-LNP is initiated under the supervision of a physician knowledgeable in the management of amyloidosis.

It is given as a drip into a vein ('intravenous infusion') usually over about 80 minutes. The usual dose of patisiran-LNP is 300 micrograms per kilogram of body weight given once every 3 weeks.

Before each infusion of patisiran-LNP, the patient will be given approved medicines that help to lower the risk of infusion-related reactions. These include anti-histamines (an anti-allergy medicine), a corticosteroid (an anti-inflammatory medicine), and a pain reliever (to reduce fever). These medications will be taken at least 60 minutes before the patient receives each dose of patisiran-LNP. These medicines can cause side effects themselves, although not everybody gets them.

How does patisiran-LNP work?

Patisiran-LNP works by lowering the liver production of TTR protein.

- This means there is less TTR protein in the blood that can form amyloid.
- This can help to reduce the effects of this illness.

Patisiran-LNP is used in adults only.

How has patisiran-LNP been studied?

The principal study relevant to the EAMS approval was a controlled trial conducted in 225 adult patients (148 patients having received patisiran-LNP and 77 having received placebo, i.e. a dummy treatment) for a period of 18 months. These patients presented with neurologic impairment and many also had cardiac involvement. Patients who were in a wheelchair or bedbound (also known as stage 3 patients) were not included in the study. Effects on the nervous system were assessed using the modified Neuropathy Impairment Score (mNIS+7), which assesses motor strength/weakness, reflexes and blood pressure; this was evaluated in patients taking patisiran-LNP and compared with that in patients taking placebo (dummy medicine) at the end of treatment. Neither the patients nor the doctors were aware of the identity of the treatment being administered during the study, placebo or patisiran-LNP, a trial design known as "randomised, double-blind design". Other assessments such as quality of life and the effect on the heart were also included.

What are the benefits and risks of patisiran-LNP?

Benefits

The levels of the protein TTR in the blood were reduced after treatment with patisiran-LNP.

In the main study, after 18 months, the mNIS+7 score in patients treated with patisiran-LNP was significantly lower than for those treated with placebo indicating a clear positive effect in these patients. Improvements were also seen in a number of other measures such as those investigating overall functioning, quality of life or heart structure and function. Mortality was also reduced.

Risks

The main risk with the treatment with patisiran-LNP relates to its route of administration as the product is given as a drip into a vein (called an 'intravenous infusion'). Reactions may occur linked to the infusion and may include symptoms such as swelling or redness at or near the infusion site, feeling short of breath, chest discomfort, rapid heart rate or dizziness.

Before each infusion additional medicines are given to lower the chance of infusion-related reactions. If the patient has an infusion-related reaction, their doctor or nurse may have to slow down or stop the infusion, and the patient may need to take other medicines to help alleviate the infusion related reactions. When these reactions stop, or get better, their doctor or nurse may decide to start the infusion again.

Treatment with patisiran-LNP may lower the amount of vitamin A in the blood. It is therefore considered necessary to take vitamin A supplements every day.

Why has patisiran-LNP been given a positive Early Access to Medicine Scientific opinion?

Only limited treatment options are available for adult patients with hATTR amyloidosis.

Liver transplant is restricted in terms of access and it is mainly effective in patients where the condition started at an early age (< 50 years of age) and with a short duration before the transplant. Tafamidis, a medicine given orally, is only indicated in patients where the condition is not yet very severe. Patients in England and Wales do not have access to tafamidis.

In view of the unmet medical need, the promising results of the principle study and the current safety data, the benefit to patients was viewed to outweigh the risks and early access to patisiran-LNP for adult hATTR patients as defined in the scope of the EAMS indication is justified.

What are the uncertainties?

As stated above, only hATTR amyloidosis patients with stage 1 or stage 2 neurologic impairment were included in the principal study. Whether patients with more severe impairment of the nerves or of the heart will benefit from treatment is not fully established. However, it is considered that the currently available data are sufficient to include these patients in the EAMS indication.

Are there on-going clinical studies for this medication?

One long-term study in patients who had been included in the principal study is ongoing. This study is planned to run over 5 years and the first results are expected within 3 years.

What measures are in place to monitor and manage risks?

A risk management plan has been developed to ensure that patisiran-LNP is used as safely as possible. Based on this plan, the company that makes patisiran-LNP must ensure that all healthcare professionals and patients in the EAMS are given information on the known risks of the medicine including its side effects and advice on reducing these risks where possible.

Information will be collected about patients before they enter the scheme. Healthcare professionals will be asked by the Company to report adverse effects experienced by patients receiving patisiran-LNP through the scheme. These safety data will be reviewed and reported to the MHRA on a regular basis by the Company.

Additional data will be collected on clinical efficacy and quality of life on a voluntary basis and subject to additional patient consent.

Withdrawn