Early Access to Medicines Scientific Opinion - Public Assessment Report
Oxervate
Treatment of moderate or severe neurotrophic keratitis
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EAMS 32162/0001

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: http://www.gmc-uk.org/mobile/news/14327

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Oxervate

What is Oxervate?

Oxervate contains the active substance cenegermin, a recombinant form of human nerve growth factor (rhNGF).

What is Oxervate used to treat/diagnose/prevent?

In the context of the Early Access to Medicines Scheme, the indication for Oxervate is 'Treatment of moderate (persistent epithelial defect) or severe (corneal ulcer) neurotrophic keratitis in adults'.
Neurotrophic keratitis is a degenerative corneal disease arising from impaired trigeminal corneal innervation leading to a decrease or absence of corneal sensation. The most common causes of this disease are herpetic infections of the cornea, surgery for trigeminal neuralgia and surgery for acoustic neuroma. Loss of corneal sensory innervation may lead to breakdown of the corneal epithelium and poor corneal healing, and subsequent ulceration, infection, melting, and perforation.
The Mackie classification describes 3 stages of severity of neurotrophic keratitis:

- Stage 1 is characterized by punctate keratopathy and/or corneal epithelial hyperplasia.
- Stage 2 is characterized by a persistent epithelial defect.
- Stage 3. is characterized by stromal involvement with a corneal ulcer that may progress to stromal melting and perforation

Despite early diagnosis and treatment to prevent progression, neurotrophic keratitis may progress to stage 3 disease which demands immediate attention to prevent stromal lysis and perforation. Permanent decrease in visual acuity from corneal scarring and astigmatism may occur.

How is Oxervate used?

Oxervate is delivered as 20µg/ml preservative-free sterile eye drop solution (ophthalmic solution). It is presented in vials for daily use, with 1 drop being administered 6 times daily, after a 2-hour interval from the previous administration.

How does Oxervate work?
Oxervate is intended to allow restoration of corneal integrity.
that has been damaged in the context of neurotrophic keratitis.

How has Oxervate been studied?
In the context of the Early Access to Medicines Scheme, Oxervate was investigated in two phase II studies described as pivotal, study NGF0212 and study NGF0214:

- Study NGF0212: a Phase I/II, double-masked, randomized, multi-centre, vehicle-controlled, parallel group study that consisted of 2 periods: An 8-week Phase I/II controlled treatment period and a 48- or 56-week follow-up period. A total of 156 patients were randomized in 32 centres in 6 EU countries: 52 patients to rhNGF 10µg/ml, 52 patients to rhNGF 20µg/ml and 52 patients to the vehicle group (vehicle without methionine).
- Study NGF0214 was conducted in the USA as an 8-week multicentre, randomized, vehicle controlled, double-masked, parallel-group study followed by a 24- or 32-week follow-up period. A total of 48 patients were randomized: 24 patients to rhNGF 20µg/ml and 24 patients to the vehicle group.

The main measure of effectiveness in both studies was the achievement of complete healing of the persistent epithelial defect or corneal ulcer, defined as the greatest diameter of the corneal fluorescein staining in the area of the persistent epithelial defect or corneal ulcer measured at the baseline visit being less than 0.5 mm at the Week 8 visit, as assessed by the central reading centre evaluating the clinical pictures.

What are the benefits and risks of Oxervate?
Benefits
After 8 weeks of treatment, more patients treated with rhNGF than those treated with the vehicle achieved complete corneal healing as determined by a central reading centre.

- In Study NGF0212 complete corneal healing was achieved by 74.5% in 10µg/ml vs 74% in 20µg/ml vs 43.1% in vehicle groups. Both doses were statistically superior to the vehicle (both p<0.002). No differences between doses were shown.
- In Study NGF0214 69.6% of patients on rhNGF 20µg/ml achieved complete healing compared to the 29.2% rate of patients receiving vehicle (p=0.006).

Risks
Eye pain was the most common adverse event. Increased lacrimation ocular hyperaemia, foreign body sensation and photophobia were also recorded.

Why has Oxervate been given a positive Early Access to Medicine Scientific opinion?
Persistent epithelial defect of the cornea and corneal ulceration are debilitating conditions that may progress to permanent loss of corneal transparency, perforation and loss of the eye. Oxervate is a pharmacological treatment that promotes corneal epithelial healing. At present there is no such drug therapy available in the UK. Successful treatment will lead to a reduced number of clinic attendances and a reduced need for surgery. Oxervate therefore offers a major advantage over methods currently available in the UK.

The MHRA has considered the benefits of Oxervate in the treatment of moderate or severe neurotrophic keratitis and concluded that the benefits are greater than the risks.

What are the uncertainties?
Even though Oxervate administration provided benefits to patients in terms of corneal healing, there

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were high rates of withdrawal from both pivotal studies due to adverse events.

- In Study NGF0212, 28.8% of patients in the rhNGF 10µg/ml group, 30.8% in the rhNGF 20µg/ml group and 23.1% in the vehicle group withdrew.
- In Study NGF0214, 25% in the rhNGF 20µg/ml group and 37.5% in the vehicle group discontinued.

Statistically significant improvements in functional outcomes such as visual acuity or corneal sensitivity were not apparent during the study periods. Whether functional outcomes improve over the longer term may be clarified when the company submits long-term data on follow-up.

Are there on-going clinical studies?
The company has committed to supplying long-term safety data as a follow-up measure.

What measures are in place to monitor and manage risks?
A risk management plan has been developed to ensure that Oxervate is used as safely as possible. Based on this plan, the company that makes Oxervate must ensure that all healthcare professionals expected to use the medicine, as well as patients, are provided with information on the medicine including the side effects of treatment and recommendations for preventing or minimizing these side effects.
Information will be collected about patients before they enter the scheme. The company will ask the healthcare professionals to report adverse events experienced by patients receiving Oxervate through the scheme. These safety data will be reviewed and reported to the MHRA on a regular basis by the Company.

Other information about Oxervate – see EAMS Treatment Protocol

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