Early Access to Medicines Scientific Opinion - Public Assessment Report
Raxone 150 mg film-coated tablets (idebenone)
As treatment for slowing the decline of respiratory function in patients with Duchenne Muscular Dystrophy (DMD) from the age of 10 years who are currently not taking glucocorticoids. The decline of respiratory function must be confirmed by repeated measurements of pulmonary function prior to initiation of treatment. Raxone can be used in patients previously treated with glucocorticoids or in patients in whom glucocorticoid treatment is not tolerated or is considered inadvisable.
Santhera Pharmaceuticals
EAMS number 46555/0001

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

What is Raxone?

Raxone is a medicine that contains a substance called idebenone in tablet form. Idebenone is a potent anti-oxidant and is believed to improve the functioning of mitochondria (important for the generation of cellular energy) inside cells.

What is Raxone used to treat?

Raxone is already licensed as a medicine to treat a rare eye condition called Leber's hereditary optic neuropathy (LHON). Under EAMS it is being made available as an unlicensed medicine to slow the decline in respiratory (lung) function in patients with Duchenne's muscular dystrophy (DMD), a degenerative disease of the muscles. It is only given to patients not taking glucocorticoids (steroids) who in addition have clear evidence of deteriorating lung function in tests that are routinely conducted by specialists involved in the care of DMD patients. Patients may not notice breathing difficulties at this stage but this becomes inevitable with time, if left untreated.

The aim of Raxone treatment is to slow down the weakening of muscles involved in respiration and, with this, potential slowing of the emergence of serious breathing difficulties in later stages of the disease. It may take some considerable time for these longer term benefits to become evident given the slow rate of progression of the disease. Early treatment may be warranted to prevent complications related to respiratory muscle weakening such as infection (pneumonia) and low oxygen levels (hypoxia). Raxone is only given to patients 10 years and older, the age range when decline in lung function becomes apparent. Lung function decline must be confirmed by spirometry (which measures the maximum flow and amount of air that can be exhaled in one breath) before Raxone is given. Raxone is given without glucocorticoids and is only given to patients previously treated with glucocorticoids such as prednisolone or deflazacort, or in patients who are not candidates for continuation or commencement of glucocorticoid treatment. This group of patients represents those

with the highest unmet need for whom no other medicinal treatment options are currently available.

How is Raxone used?
Raxone 150 mg film-coated tablets are taken by mouth with food. If a patient has difficulty in swallowing, tablets can if necessary be crushed into semi-solid or liquid feed for administration through a tube into the stomach. The recommended dose for DMD patients is two tablets taken three times a day (900 mg per day in total). There is no specified limit on the length of time that Raxone can be taken for. However, there are limited data beyond 12 months of use.

How does Raxone work?
In DMD, deficiency of the dystrophin protein in muscle tissue causes disturbance in mitochondria inside cells, sometimes referred to as the "powerhouses" of the cell due to their involvement in energy generation. Idebenone is thought to help restore mitochondrial energy generation and more generally to provide anti-oxidant protection from reactive oxygen species (ROS). The deficiency in dystrophin protein occurs regardless of which mutation the patient may be carrying in their dystrophin gene. In principle therefore Raxone has potential to be of benefit in a broad population of DMD patients, once respiratory decline has commenced.

How has Raxone been studied?
Raxone has been studied in a limited number of DMD patients (53 DMD patients in total having received Raxone with 42 patients having received placebo i.e. dummy treatment). The principal study relevant to the EAMS approval was a controlled trial conducted in 67 patients for a period of 12 months in which respiratory function measured by spirometry in patients taking Raxone was compared with that in patients taking placebo (dummy medicine). Neither the patients nor the doctors were aware of the identity (placebo or Raxone) of the treatment being administered during the study (randomised double blind design). None of the patients were taking glucocorticoids. Spirometry data over a period of 12 months were also compared with that from patients matched for key characteristics in a contemporaneous Natural History Dataset from the Cooperative International Neuromuscular Research Group (CINRG).
Raxone has been investigated in other diseases and, across all indications, clinical study data are available for up to three years of treatment at doses up to 2250 mg /day in 439 patients in total.

What are the benefits and risks of Raxone?
Benefits
Raxone slows the decline in lung function, measured by spirometry. This was most clearly demonstrated by "slope analyses" that measure the gradient of decline in lung function which is more able to discern benefit when there is a slow but predictable rate of decline in respiratory function, as is the case in DMD. The data are summarised in tabular form in section 5.1 of the EAMS Healthcare Professional Treatment Protocol. Spirometry provides a surrogate means of evaluation in the clinical context of DMD due to the slowness of respiratory decline and therefore overt breathing difficulties may take several years to become apparent. The comparison with the CINRG dataset is consistent with Raxone slowing the decline. There are some other supportive data suggesting a possible reduction in serious respiratory infections and antibiotic use but the available data to date are not conclusive. In the meantime, the lung function data are considered to support the potential for long term benefit.

Risks
Raxone is considered overall to have an acceptable safety profile. Diarrhoea is the commonest adverse effect but this is mainly of mild to moderate severity and in the clinical trials generally did not cause patients to discontinue treatment. From clinical trials in other diseases, there may be risk of liver

inflammation which cannot be discounted as a risk in DMD. There may also be a risk of low blood count.

Why has Raxone been given a positive Early Access to Medicine Scientific opinion?
Patients with DMD who have progressed to the stage of respiratory decline, and who are not receiving glucocorticoids, have no treatment options available to them, other than supportive care. Although Translarna (ataluren) is available for the treatment of DMD patients with a so-called nonsense mutation in the dystrophin gene it is restricted to those patients who are ambulatory (still able to walk). DMD patients who are in respiratory decline will be largely unable to walk and will therefore not be eligible to receive ataluren. In a small study of DMD patients treated with Raxone for 12 months there was evidence of benefit on lung function that might, over the longer term, help to delay the onset of serious respiratory complications. With any small study, there is always uncertainty whether the benefit and risks will be replicated more widely in the proposed target population. To address this uncertainty the Company conducted a variety of analyses to test the robustness of the data within the limitations of a small study and there was no evidence that the small sample had been non-representative of a larger population. No serious safety concerns have emerged.

In conclusion, considering the very high level of unmet need in this patient population, and that the benefits outweigh the risks, early access to Raxone for DMD patients as defined in the scope of the EAMS indication is considered to be justified.

What are the uncertainties?
As stated above, there is always uncertainty with any small study. There is also uncertainty in relation to the use of spirometry as a surrogate means of evaluation in the context of a slowly progressive respiratory function deficit. There is also a limited amount of long term safety data at a dose of 900 mg daily. The possibility of cumulative long term safety issues therefore cannot be discounted. Ongoing safety evaluation is a requirement under EAMS (see below) and adverse event monitoring will include ongoing respiratory function evaluation. As a requirement of EAMS, any safety data – whether within or outside EAMS reporting requirements - that informs an alteration in benefit-risk must be communicated to the MHRA. The uncertainties are therefore considered to be acceptable.

Are there on-going clinical studies?
There is an ongoing study of Raxone to investigate respiratory function in DMD patients who are taking Raxone along with glucocorticoids, compared with those who are taking glucocorticoids alone. These patients are therefore not candidates to receive Raxone under EAMS. However, the data may ultimately be informative for patients within the scope of the EAMS indication.

What measures are in place to monitor and manage risks?
A risk management plan has been developed to ensure that Raxone is used as safely as possible. Based on this plan, the Company that makes Raxone must ensure that all healthcare professionals and patients in the EAMS are given information on the known risks of idebenone 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 Raxone through the scheme. These safety data will be reviewed and reported to the MHRA on a regular basis by the Company.
Patients in the EAMS will also receive an alert card from their doctor summarising the important risks with the medicine and the details of their treating specialist. Patients should carry the card with them at all times in case they need treatment or advice from a healthcare professional who is not familiar with Raxone treatment.

Other information about Raxone – see EAMS Treatment Protocol