

RENEWAL of Early Access to Medicines Scientific Opinion – ANNEX to Public Assessment Report. The renewal is effective from 21st June 2018 and is valid for 12 months.

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: <https://www.gmc-uk.org/guidance/28349.asp>

Background

An EAMS scientific opinion was granted by the MHRA on 21st June 2017 for Raxone 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 basis of the decision is described in the Public Assessment Report:

<https://www.gov.uk/government/publications/early-access-to-medicines-scheme-eams-scientific-opinion-raxone-to-treat-the-decline-of-respiratory-function-in-patients-with-duchenne-muscular-dys>

In January 2018 the European Medicine Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) decided against approving a variation to the Raxone drug licence to add the indication of respiratory decline in patients with DMD, on the grounds that the available data were limited and could not be robustly interpreted.

http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/003834/WC500234840.pdf

EAMS Scientific Opinion

The UK Commission on Human Medicines (CHM) re-considered the EAMS scientific opinion for Raxone in April 2018, subsequent to the refusal of the variation to the marketing authorisation by the EMA. It is recognised that the regulatory requirements for granting an EAMS scientific opinion can differ

from those for a marketing authorisation in some circumstances. A Patient Group Meeting was also held ahead of the CHM review to gain a full understanding of the patient perspective. The patient meeting was attended by Duchenne Muscular Dystrophy patients, patient representatives, Commissioners and representatives from the MHRA.

CHM observed that no new efficacy data or safety concerns had emerged during the EAMS period.

In re-reviewing the data that supported the EAMS scientific opinion, CHM acknowledged that the small size of the study still presents a theoretical risk that there has been bias due to chance inclusion of patients destined to do better in the Raxone arm. A larger confirmatory dataset will lessen the risk of such bias and the Company is on schedule to provide this.

CHM also acknowledged uncertainty in relation to whether respiratory benefit would be maintained over the longer term due to the limitations of the clinical evidence. Preliminary evidence of reduced antibiotic use and incidence of respiratory infections were nonetheless considered supportive of the potential for ongoing respiratory benefit.

While acknowledging the uncertainties, CHM advised that the EAMS scientific opinion should be upheld, taking the following into consideration: i) the high level of unmet need as clearly described in the patient group meeting; ii) the promising early data are consistent with positive benefit-risk; iii) the medicine has an acceptable level of tolerability and there are no serious safety concerns; iv) definitive data to inform a robust conclusion on efficacy and safety are anticipated; v) a new marketing authorisation application for idebenone in the EAMS indication is planned for 2019; and vi) ongoing patient monitoring is a requirement of EAMS.

CHM further advised that renewal of the EAMS scientific opinion could proceed as scheduled on 21st June 2018, subject to the Company satisfactorily addressing a number of recommendations.

EAMS Renewal

CHM made a number of recommendations for implementation in the subsequent EAMS period.

CHM recommended the implementation of clinical effectiveness monitoring in line with the latest clinical practice guidelines, which the Company has agreed to. As well as providing additional data for real world evaluation, ongoing benefit-risk monitoring at an individual patient level will help to ensure that treatment is not continued in patients who are not obtaining meaningful benefit.

CHM also recommended that the need for patients to be in active respiratory decline – specified in the EAMS indication - should be reinforced in the EAMS documentation provided to the treating physician. The active compound, idebenone, is surmised to protect viable muscle tissue by improvement in mitochondrial functioning but repair of fibrosed muscle at a late stage of disease would not be expected.

The Company now proposes an enrolment criterion of percent predicted FVC within the range 80-25% to ensure that patients enrolled to receive Raxone through EAMS will be in active respiratory decline. This is agreed as an appropriate range to ensure that patients have entered the stage of respiratory decline where benefit of treatment with idebenone can be measured. This range of FVC could also include some patients who require nocturnal ventilation. However, patients who are receiving diurnal ventilation are not eligible to enrol in EAMS as these patients are likely to have reached a very low level of lung function that has not been previously studied with this medicine.

It is acknowledged that some DMD patients have a level of cognitive impairment that hinders reliable spirometry evaluation and in such cases it is acceptable for the treating physician to use clinical judgement to diagnose active respiratory decline.

Amendments have been made to the drug interaction section of the Healthcare Professional and Patient EAMS Treatment Protocols, in line with changes made to the existing product licence for Raxone in the indication of Leber's hereditary optic neuropathy.

The recommendations made by CHM are considered to have been satisfactorily addressed. The scope of the EAMS indication remains the same. The confirmation of active respiratory decline is clarified in the EAMS enrolment procedure.

The EAMS scientific opinion is renewed from 21st June 2018 for a further twelve months. The medicine will continue to be subject to the compulsory EAMS reporting requirements, with periodic reporting of adverse event data. The Company is also obliged to inform the MHRA of any alteration in benefit-risk.

WITHDRAWN