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Information for NHS Medical Directors

Regarding EAMS scientific opinion for

Risdiplam is indicated for the treatment of patients 2 months of age and older with type 1 and type 2 spinal muscular atrophy (SMA) who are not suitable for authorised treatments.

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising unlicensed medicines to UK patients that have a high unmet clinical need. A positive scientific opinion is only issued by the MHRA if the criteria for the EAMS are fulfilled, which includes demonstrating a positive benefit risk balance (quality, safety and efficacy assessment) and the ability of the pharmaceutical company to supply a medicine according to a consistent quality standard.

EAMS medicines are unlicensed medicines. The term 'unlicensed medicine' is used to describe medicines that are used outside the terms of their UK licence or which have no licence for use in the UK. GMC guidance on prescribing unlicensed medicines can be found below:

<https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/prescribing-and-managing-medicines-and-devices/prescribing-unlicensed-medicines>

The opinion is based on assessment of the information supplied to the MHRA on the benefits and risks of the medicine. As such this is a scientific opinion and should not be regarded as a licensed indication or a future commitment by the MHRA to licence such a medicine, nor should it be regarded as an authorisation to sell or supply such a medicine. A positive scientific opinion is not a recommendation for use of the medicine and should not be interpreted as such. Under EAMS the risk and legal responsibility for prescribing a 'special' remains with the physician, and the opinion and EAMS documentation published by the MHRA are intended only to inform physicians' decision making and not to recommend use. An EAMS scientific opinion does not affect the civil liability of the manufacturer or any physician in relation to the product.

EAMS procedural assessment at the MHRA

A full assessment of the quality, safety and efficacy of risdiplam has been conducted by the MHRA's assessment teams, including pharmacists, toxicologists, statisticians, pharmacokinetic and medical assessors. This assessment process also includes consideration of the quality, safety and efficacy aspects by the UK independent expert committees including Expert Advisory Groups (EAGs) and the Commission on Human Medicines (CHM):

- The Commission on Human Medicines (CHM) advises ministers on the quality, safety and efficacy of medicinal products. The Chair and Commissioners are appointed in accordance with the Code of Practice for Ministerial Appointments to Public Bodies. The Chair and Commissioners follow a code of practice, in which they are precluded from holding personal interests. The Commission is supported in its work by Expert Advisory Groups (EAGs), covering various areas of medicine.

<https://www.gov.uk/government/organisations/commission-on-human-medicines/about>

- Chemistry, Pharmacy and Standards EAG, which advises the CHM on the quality in relation to safety and efficacy of medicinal products

<https://www.gov.uk/government/organisations/commission-on-human-medicines/about/membership#chemistry-pharmacy-and-standards-eag>

Pharmacovigilance system

A pharmacovigilance system for the fulfilment of pharmacovigilance tasks has been put in place for this EAMS medicine, including a risk management plan. As the safety profile of the EAMS medicine is not fully established it is particularly important that any harmful or unintended responses to EAMS medicines are reported. Healthcare professionals should be aware of their obligations to report adverse event information upon enrolment of any patients receiving EAMS medicines in the scheme. They will be required to follow the process which the pharmaceutical company which manufactures the EAMS medicine has in place to enable systematic collection of information on adverse events.

For more detailed information on this EAMS medicine, please refer to the Public Assessment Report, EAMS treatment protocol for healthcare professionals, EAMS treatment protocol for patients and EAMS treatment protocol for pharmacovigilance.

<https://www.gov.uk/government/collections/early-access-to-medicines-scheme-eams-scientific-opinions>

Justification for the fulfilment of the EAMS criteria

There are four EAMS criteria that need to be fulfilled before a medicine can enter the scheme and a positive scientific opinion is issued by the MHRA. The fulfilment of the criteria for this particular medicine is described below.

1	<p>(a) Life threatening or seriously debilitating condition</p> <p>Spinal Muscular Atrophy (SMA) is a monogenic neuromuscular disorder resulting in severe weakness of the limbs, trunk, bulbar and respiratory muscles secondary to failure to gain and maintain functional motor nerve innervation of skeletal muscles. SMA is characterized by the dysfunction of alpha motor neurons within the anterior horn of the spinal cord, leading to skeletal muscle weakness and atrophy.</p> <p>It is the leading genetic cause of mortality in infants and young children, with an estimated incidence of 1 in 6,000 to 1 in 10,000 live births and carrier frequency of 1 in 40-60 individuals.</p> <p>(b) High unmet need: existing methods/licensed medicines have serious limitations</p> <p>Nusinersen (Spinraza[®]) is indicated for the treatment of 5q Spinal Muscular Atrophy". It is administered by lumbar puncture, initially with 4 loading doses on Days 0, 14, 28 and 63, followed by routine maintenance doses every 4 months. The administration of Spinraza[®] may be limited in patients who cannot have repeated lumbar punctures; also, the incidence of hydrocephalus may require withdrawal of treatment.</p> <p>Onasemnogene abeparvovec (Zolgensma[®]) is a gene therapy medicinal product that expresses the human survival motor neuron (SMN) protein. It is a solution for infusion (2 x 10¹³ vector genomes/ml) and is indicated in the treatment of patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene. An immune response to the adeno-associated viral vector serotype 9 (AAV9) capsid will occur after administration of onasemnogene abeparvovec. This can lead to elevations in liver transaminases, elevations of troponin I, or decreased platelet counts. To dampen the immune response immunomodulation with corticosteroids is recommended. Where feasible, the patient's vaccination schedule should be adjusted to accommodate concomitant</p>
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	<p>corticosteroid administration prior to and following onasemnogene abeparvovec infusion.</p>
2	<p>The medicinal product offers major advantage over existing methods in the UK</p> <p>In type 1 SMA, 29.3% (95% CI: 17.8%, 41.3%) of patients were sitting without support after 12 months of treatment at the proposed dose, as assessed by Item 22 of the Bayley Scales of Infant and Toddler Development – Third Edition (BSID-III) gross motor scale. This proportion is significantly higher than the pre-defined performance criterion of 5% based on natural history data ($p < 0.0001$). Further:</p> <ul style="list-style-type: none"> - 85.4% (95% CI: 73.4%, 92.2%) of patients were free of medical event such as permanent ventilation defined as tracheostomy or ≥ 16 hours of non-invasive ventilation per day or intubation for > 21 consecutive days in the absence of, or following the resolution of, an acute reversible event, against the pre-defined performance criterion of 42% without treatment ($p < 0.0001$) - And 87.8% (76.1%, 95.1%) of patients were able to swallow <p>In type 2 SMA, when compared to placebo, patients treated with risdiplam demonstrated a significant improvement in primary analysis for the pivotal study at the proposed dose, which was the change from baseline score on the Motor Function Measure-32 (MFM32) scale after 12 months of treatment (1.55 points mean difference; 95% CI: 0.30, 2.81, $p = 0.0156$). Patients 2-5 years old treated with risdiplam demonstrated the greatest improvement on MFM32 compared to placebo control (≥ 3 points increase in 78.1 % vs 52.9 %). Patients ≥ 18 years old treated with risdiplam achieved stabilization of disease (change from baseline MFM32 total score ≥ 0 point(s): 57.1% vs. 37.5%). Consistent improvement compared to baseline MFM32 was observed in both Type 2 and 3 SMA patients (1.54 points [95% CI: 0.06, 3.02]; 1.49 points [95% CI: -0.94, 3.93] respectively) treated with risdiplam compared to placebo control.</p> <p>Therefore it is considered that risdiplam offers major advantages for patients aged 2 months and older with type 1 and type 2 SMA who are not suitable for approved products.</p>
3	<p>The potential adverse effects of the medicinal product are outweighed by the benefits, allowing for a conclusion of a positive benefit/risk balance</p> <p>The main adverse events (occurring $\geq 10\%$) reported in type 1 SMA include upper respiratory tract infection, pyrexia, pneumonia, constipation, nasopharyngitis and rhinitis.</p> <p>In the SMA type 2 the main adverse drug reactions are diarrhoea, rash and arthralgia. Rash includes rash, rash maculo-papular, erythema, dermatitis allergic, rash erythematous, folliculitis, rash popular.</p> <p>In conclusion, the benefit/risk for risdiplam in the present indication is positive.</p>
4	<p>The company is able to supply the product and to manufacture it to a consistent quality standard, including the presence of appropriate GMP certification.</p> <p>The company has provided all documentation necessary to prove that the EAMS medicine is manufactured/packaged according to GMP.</p>