Medicines Management Programme

Managed Access Protocol – Risdiplam

(Evrysdi®) for the treatment of 5q Spinal Muscular Atrophy

Approved by:	Prof. Michael Barry, Clinical Lead, MMP.
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Table of Contents

Tables

List of Abbreviations

BSID-III	Bayley Scales of Infant and Toddler Development Third Edition
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CMAP	Compound muscle action potential
HINE	Hammersmith Infant Neurological Examination
HSE	Health Service Executive
HTH	High Tech Hub
MAP	Managed Access Protocol
MFM	Motor Function Measure
MMP	Medicines Management Programme
mRNA	Messenger ribonucleic acid
NIV	Non-invasive ventilator
PCRS	Primary Care Reimbursement Service
RHS	Revised Hammersmith Scale
RULM	Revised Upper Limb Module
SMA	Spinal Muscular Atrophy
SMN	Survival motor neurone
SmPC	Summary of product characteristics

1. Risdiplam

Risdiplam is a survival of motor neuron 2 (SMN2) pre-messenger ribonucleic acid (m-RNA) splicing modifier, designed to treat Spinal Muscular Atrophy (SMA) caused by mutations of the SMN1 gene in chromosome 5q that lead to SMN protein deficiency.[i] Functional SMN protein deficiency is directly linked to the SMA pathophysiology which includes progressive loss of motor neurons and muscle weakness. Risdiplam corrects the splicing of SMN2 to shift the balance from exon 7 exclusion to exon 7 inclusion into the mRNA transcript, leading to an increased production of functional and stable SMN protein. Thus, risdiplam treats SMA by increasing and sustaining functional SMN protein levels.

From 1st September 2023, one presentation of risdiplam is available under the High Tech Arrangement as:

- ▼ Evrysdi® 0.75 mg/mL powder for oral solution 60 mg bottle

1.1 Licensed indication

Risdiplam is indicated for the treatment of 5q SMA in patients two months of age and older, with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies.[ii]

1.2 Reimbursement

Conditional reimbursement of Evrysdi® on the High Tech Arrangement under this protocol is confined to the following subgroup of the licensed population:

- Patients with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 who are aged between two months and < 18 years of age.

Reimbursement of Evrysdi® is conditional on its use as monotherapy in the treatment of SMA.

1.3 Licensed dose

Evrysdi® is supplied in a bottle which contains 60 mg risdiplam in 2 g powder for oral solution. Once constituted, the 80 ml solution contains 0.75 mg risdiplam per mL. Please refer to the Summary of Product Characteristics (SmPC) for more information on reconstitution and posology.

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[i] Where the SMN1 gene becomes non-functional and is unable to produce the SMN protein, this is known as 5q-SMA. Mutations in other genes can also cause SMA; such cases of SMA are known as 'non-5q SMA'. Due to the rarity of 'non-5q SMA', 5q-SMA will be referred to as SMA throughout this document.

[ii] Please refer to the summary of product characteristics for Evrysdi® for full prescribing information.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

The recommended dose of Evrysdi® is determined by age and body weight. Evrysdi® is taken orally once a day after a meal, at approximately the same time each day.

Table 1: Licensed dosing of risdiplam (Evrysdi®) for the treatment of 5q SMA by age and body weight

Age and body weight	Recommended daily dose
2 months to < 2 years of age	0.20 mg/kg
≥ 2 years of age (< 20 kg)	0.25 mg/kg
≥ 2 years of age (≥ 20 kg)	5 mg

mg: milligram, kg: kilogram

Treatment with a daily dose above 5 mg has not been studied.

If a patient is recommended for reimbursement of risdiplam, reimbursement will be supported in line with the licensed dose as per SmPC. As the dose is weight dependent, and treatment with a daily dose above 5 mg has not been studied (i.e. patients ≥ 20 kg), the maximum quantity reimbursed will be three bottles monthly of Evrysdi® 0.75 mg /mL powder for oral solution. However, given the maximum dose and the expiry date on reconstitution (64 days), it is anticipated that the maximum quantity required will be 31 bottles annually.

1.4 Application Process

Approved prescribers are required to apply for reimbursement approval on an individual patient basis. The *Application form for Medicines for the Treatment of Spinal Muscular Atrophy (SMA)* should be completed and sent[iii] by secure email to the Medicines Management Programme (MMP) at mmp@hse.ie .

See section 2 for further details on Reimbursement Criteria- Initiation.

If a patient is approved for reimbursement by the MMP, the High Tech prescription for risdiplam should be generated on the High Tech Hub (HTH). High tech prescriptions which are not hub generated will not be eligible for reimbursement by the Health Service Executive (HSE)-Primary Care Reimbursement Service (PCRS).

[iii] Post: Prof. Michael Barry, HSE-Medicines Management Programme, Department of Pharmacology and Therapeutics, Trinity Centre for Health Sciences, St James's Hospital, Dublin 8

1.5 Reimbursement Price

The reimbursement price of the presentation of Evrysdi® available on the High Tech Arrangement as of 1st September 2023, is as follows:

Table 2: Reimbursement price of the presentation of risdiplam available on the High Tech Arrangement

Strength (pack size)	**Reimbursement**	
Evrysdi® 0.75 mg/mL Powder for Oral Solution 60mg bottle (80mL)	**Code**	**Price**
	89292	€8,988.31 *

mL: Millilitre, mg: Milligram; * price is correct as of 1st September 2023

A commercial in confidence arrangement is in place with the marketing authorisation holder to reduce the net acquisition cost of Evrysdi® to the HSE.

2. Reimbursement criteria - Initiation

This section outlines the criteria that must be satisfied in order for a patient to be recommended for reimbursement of risdiplam for the treatment of 5q-SMA under the High Tech Arrangement.

2.1 Prescribers

The prescribing of risdiplam under the High Tech Arrangement is confined to consultant neurologists with experience in the diagnosis and management of SMA in specialist centre(s) in Ireland, who have agreed to the terms of this Managed Access Protocol (MAP) and have been approved by the HSE.

Applications for reimbursement approval will only be considered from these prescribers.

2.2 Diagnosis

For a positive reimbursement recommendation, clinicians are required to confirm a diagnosis of 5q SMA Type I, Type II or Type III.

2.2.1 Genetic testing

Confirmed genetic diagnosis of 5q SMA is a condition of reimbursement. A copy of the genetic test should be included with the application for reimbursement approval.

2.2.2 Patient age

Applications for reimbursement approval will only be considered in individuals aged between two months and < 18 years of age at time of application.

2.2.3 Patient weight

The weight of the patient should be outlined in the application.

2.3 Patient's medical treatment

Clinicians are required to provide details of the patient's medical treatment at the time of application including any previous therapies used in the treatment of SMA. Reimbursement of Evrysdi® will be conditional on its use as monotherapy in the treatment of SMA.

Where a patient has prior approval for nusinersen, if there is a desire to switch to risdiplam, a new application for risdiplam must be submitted and the individual must continue to meet the eligibility criteria for nusinersen at the time of application. Patients who meet the discontinuation criteria for nusinersen are not eligible for reimbursement with risdiplam.

2.4 Patient's physical presentation

Clinicians are required to provide details of the patient's physical presentation at the time of application e.g. limb function, speech, ability to sit unaided, roll, body strength, any supplementary requirements/supports. Clinicians may be asked to provide compound muscle action potential (CMAP) results.

2.5 Assessment scales

Clinicians are required to provide details of the proposed assessment scale(s) and document baseline measurements for same. The appropriate scale(s) is/are determined at baseline prior to the initiation of therapy and is/are based on the patient's motor ability. Appropriate scales include the following:

- Hammersmith Infant Neurological Examination (HINE)
- Revised Hammersmith Scale (RHS)
- Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)
- Bayley Scales of Infant and Toddler Development Third Edition (BSID-III)
- Motor Function Measure (MFM32)

Assessment scales may additionally include:

- Revised Upper Limb Module (RULM)

2.6 Reimbursement exclusion criteria

In line with the exclusion criteria[iv] from the FIREFISH and SUNFISH trials and the *Managed Access Agreement (ID1631*) *NICE (2021),* reimbursement of risdiplam will not be considered in:

- Patients with any contraindication to treatment as set out in the SmPC for risdiplam (Evrysdi®),
- Where the clinical and genetic diagnosis of SMA is not fulfilled,
- Patients with SMA Type 0 or Type IV*,*
- Patients requiring permanent ventilation (≥ 16 hours/day for 21 consecutive days in the absence of acute reversible infection)/tracheostomy requirement at baseline,
- Patients with additional life-limiting conditions where treatment with risdiplam would not provide long-term benefit,
- Patients receiving treatment with additional disease-modifying therapies to treat SMA,
- Patients who have been hospitalised for a pulmonary event within the last two months,
- Patients with unstable gastrointestinal, renal, hepatic, endocrine or cardiovascular system diseases,
- Pregnant or lactating women,
- Patients who have had previous treatment with nusinersen who meet the discontinuation criteria for nusinersen,
- Patients who have had successful treatment with onasemnogene abeparvovec. For the purpose of this MAP the definition of non-success of onasemnogene abeparvovec is considered to be:[v]

  (a) A **reduction in motor ability,** defined as total worsening in scale score corroborated by two consecutive measurements from any two of the following three scales:

  - > 2 points on horizontal kick or 1 point on other HINE scores excluding voluntary grasp
  - > 4 points on the CHOP INTEND scale
  - > 3 points on the RHS scale

  A scaled equivalent of these losses would apply if a domain was unmeasurable / not suitable. These scores are derived from the minimal clinical indicators of difference. For example, if a patient deteriorates on one scale (e.g. loses > 3 points on the RHS scale) but maintains

[iv] This list is not exhaustive; please refer to the summary of product characteristics for Evrysdi® for full prescribing information.

[v] NICE Technology Appraisal Guidance TA755, published 16th December 2021.

stability or demonstrates improvement on another scale that has been measured since baseline (e.g. RULM), the patient's treatment with onasemnogene abeparvovec would be considered to be successful.

AND/OR

(b) **A deterioration in respiratory function,** defined as an increasing requirement for respiratory support overnight and/or, for that patient, an uncharacteristic increase in respiratory infections requiring hospital treatment that cannot be accounted for by aspiration or intrinsic lung disease.

3. Reimbursement criteria – Discontinuation

All patients should be formally assessed at baseline and every six months thereafter.

Stopping Criteria for all patients [vi]

a. Ventilation requirements

Discontinue if permanent ventilation is required for more than 16 hours per day for 21 consecutive days in the absence of acute respiratory infection OR if there is a requirement for the insertion of permanent tracheostomy.

b. Motor function

Frequency of assessments: Formally assess at baseline and every six months thereafter.

Where one scale has been measured from baseline, discontinue if total worsening in scale score corroborated by two consecutive measurements (in order to allow for confirmation of worsening and not an 'off' assessment day) is as follows:

- > 2 points on horizontal kick or one point on other HINE scores (excluding voluntary grasp)
- > 4 points on the CHOP-INTEND scale
- > 3 points on the RHS

Where two (or more) scales have been measured from baseline discontinue if there is total worsening in scale score(s), in the absence of any stability or improvement in other scales, corroborated by two consecutive measurements (in order to allow for confirmation of worsening and not an 'off' assessment day). For example, if a patient deteriorates on one scale but maintains stability or demonstrates improvement on another scale that has been measured since baseline

[vi] NICE 2021. Managed Access Agreement. Risdiplam for treating spinal muscular atrophy in children and adults [ID1631].

(e.g. RULM) AND in the opinion of the treating clinician, the patient continues to receive clinical benefit from treatment with risdiplam then continuation of treatment may be considered.

Other Stopping Criteria for SMA Type I, II and III:

- If, in the parents' view, the quality of life is poor because of SMA disability progression or drug side effects.
- If the patient is diagnosed with an additional progressive life-limiting condition where treatment would not provide long-term benefit such as terminal cancer or catastrophic brain injury.
- Any additional unforeseen circumstances which may necessitate a discussion with the parents or patient to discontinue treatment.

Following approval of a patient for reimbursement of risdiplam under the High Tech Arrangement, the prescribing clinician will be required to submit follow-up information to the MMP, as requested. Follow-up data may be requested by the MMP for audit purposes and provision of same is a condition of ongoing reimbursement.

3.1 Follow-up data

Patients should be assessed every six months to determine the effects of risdiplam on disease progression. Outcome data, appropriate to the patient, should be submitted and sent by secure email to the MMP (mmp@hse.ie) annually when requested, outlining:

- CHOP-INTEND scores, and/or other relevant outcome measures,
- Current requirement for non-invasive ventilator (NIV) support,
- Current requirement for non-oral nutrition,
- Any changes to clinical history since initiation.

4. Prescribing of risdiplam (Evrysdi® 0.75 mg/mL powder for oral solution)

Please refer to the SmPC for risdiplam (Evrysdi®) for full prescribing information including monitoring and patient counselling requirements. Prescriptions must be generated through the HTH and only approved prescriber(s) will have access to prescribe risdiplam.

The following confirmations are required when prescribing risdiplam:

- Confirmation that risdiplam (Evrysdi®) is being prescribed for a MMP approved patient in accordance with the MAP established in line with the terms of reimbursement approval given by the HSE.

- Confirmation that the prescriber will assist the HSE/MMP in their conduct of audits* through provision of information as requested, to provide assurance that the product is being prescribed in line with HSE reimbursement approval and the MAP.
- Confirmation that the patient or their representative/guardian as appropriate, is aware that the application for reimbursement approval is being made on behalf of the patient and that audits may occur during which their personal data will be reviewed.

* Follow-up data may be requested by the HSE/MMP for audit purposes and provision of same is a condition of ongoing reimbursement.