Medicines Management Programme

Managed Access Protocol – Onasemnogene abeparvovec (Zolgensma®) for the treatment of:

- **5q Spinal Muscular Atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA type 1, or**
- **pre-symptomatic patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene**

▼ 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.

Approved by:	Prof. Michael Barry, Clinical Lead, MMP.
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CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
HSE	Health Service Executive
MAP	Managed Access Protocol
MMP	Medicines Management Programme
NIV	Non-invasive ventilator
OA	Onasemnogene abeparvovec
SmPC	Summary of product characteristics
SMA	Spinal Muscular Atrophy
SMN	Survival motor neuron gene
TMA	Thrombotic microangiopathy
vg	vector genomes

1. Onasemnogene abeparvovec

Onasemnogene abeparvovec (OA) (Zolgensma®) is a gene therapy designed to introduce a functional copy of the survival motor neuron gene (SMN1) in the transduced cells to address the monogenic root cause of the disease. By providing an alternative source of SMN protein expression in motor neurons, it is expected to promote the survival and function of transduced motor neurons.

From October 2021, OA is available under the Hospital Arrangement as:

- Zolgensma® 2x 10^{13} vector genomes(vg)/ml solution for infusion

Vials are available in two volumes containing an extractable volume of not less than either 5.5 ml or 8.3 ml. The total number of vials and combination of fill volumes in each finished pack will be customised to meet dosing requirements for individual patients depending on their weight.

1.1 Licensed indication

Zolgensma® is indicated for the treatment of 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 three copies of the SMN2 gene. This managed access protocol relates to its use in the treatment of symptomatic SMA type 1 patients, and pre-symptomatic SMA patients with up to three copies of the SMN2 gene.

1.2 Licensed dose

OA is supplied in a vial (10 mL polymer crystal zenith) with stopper (20 mm chlorobutyl rubber) and seal (aluminum, flip-off) with a coloured cap (plastic), in two different vial fill volume sizes, either 5.5 ml or 8.3 ml.

OA is given as a single-dose intravenous infusion. Patients receive a dose of nominal 1.1 x 10^{14} vg/kg OA. The total volume is determined by patient body weight.

Table 1 (overleaf) gives the recommended dosing for patients who weigh 2.6 kg to 21.0 kg. The table also includes the exact number of vials required for each patient. Please refer to the Summary of Product Characteristics (SmPC) for more information on posology and method of administration.

Table 1: Recommended dosing of OA (Zolgensma®) based on patient body weight

Patient weight range (kg)	Dose (vg)	Total volume of dose[a] (ml)	5.5 ml vial[b]	8.3 ml vial[c]	Total vials per carton
2.6 - 3.0	3.3×10^{14}	16.5	0	2	2
3.1 – 3.5	3.9×10^{14}	19.3	2	1	3
3.6 – 4.0	4.4×10^{14}	22.0	1	2	3
4.1 – 4.5	5.0×10^{14}	24.8	0	3	3
4.6 - 5.0	5.5×10^{14}	27.5	2	2	4
5.1 - 5.5	6.1×10^{14}	30.3	1	3	4
5.6 – 6.0	6.6×10^{14}	33.0	0	4	4
6.1 – 6.5	7.2×10^{14}	35.8	2	3	5
6.6 – 7.0	7.7×10^{14}	38.5	1	4	5
7.1 – 7.5	8.3×10^{14}	41.3	0	5	5
7.6 - 8.0	8.8×10^{14}	44.0	2	4	6
8.1 – 8.5	9.4×10^{14}	46.8	1	5	6
8.6 – 9.0	9.9×10^{14}	49.5	0	6	6
9.1 – 9.5	1.05×10^{15}	52.3	2	5	7
9.6 - 10.0	1.10×10^{15}	55.0	1	6	7
10.1 – 10.5	1.16×10^{15}	57.8	0	7	7
10.6 – 11.0	1.21×10^{15}	60.5	2	6	8
11.1 – 11.5	1.27×10^{15}	63.3	1	7	8
11.6 - 12.0	1.32×10^{15}	66.0	0	8	8
12.1 – 12.5	1.38×10^{15}	68.8	2	7	9
12.6 - 13.0	1.43×10^{15}	71.5	1	8	9
13.1 - 13.5	1.49×10^{15}	74.3	0	9	9
13.6 – 14.0	1.54×10^{15}	77.0	2	8	10
14.1 – 14.5	1.60×10^{15}	79.8	1	9	10
14.6 – 15.0	1.65×10^{15}	82.5	0	10	10
15.1 – 15.5	1.71×10^{15}	85.3	2	9	11
15.6 – 16.0	1.76×10^{15}	88.0	1	10	11
16.1 – 16.5	1.82×10^{15}	90.8	0	11	11
16.6 – 17.0	1.87×10^{15}	93.5	2	10	12
17.1 – 17.5	1.93×10^{15}	96.3	1	11	12
17.6 -18.0	1.98×10^{15}	99.0	0	12	12
18.1 – 18.5	2.04×10^{15}	101.8	2	11	13
18.6 – 19.0	2.09×10^{15}	104.5	1	12	13
19.1 – 19.5	2.15×10^{15}	107.3	0	13	13
19.6 – 20.0	2.20×10^{15}	110.0	2	12	14
20.1 - 20.5	2.26×10^{15}	112.8	1	13	14
20.6 – 21.0	2.31×10^{15}	115.5	0	14	14

[a] NOTE: Number of vials per kit and required number of kits is weight-dependent. Dose volume is calculated using the upper limit of the patient weight range.
[b] Vial nominal concentration is 2×10^{13} vg/l and contains an extractable volume of not less than 5.5 ml.
[c] Vial nominal concentration is 2×10^{13} vg/ml and contains an extractable volume of not less than 8.3 ml.

1.3 Reimbursement

Approved prescribers are required to apply for reimbursement approval on an individual patient basis. Applications for the individual recommendation of OA should be sent by secure email to the Health Service Executive -Medicines Management Programme (HSE-MMP) at mmp@hse.ie. *See Section 2 for further details on Reimbursement criteria.*

1.3.1 Approval Process

The following outlines the process for individual treatment approvals:

1. An individual application is submitted by the prescribing clinician to the HSE-Medicines Management Programme (MMP).

2. The HSE-MMP review the application with two possible outcomes:

    a. HSE-MMP make a positive recommendation for treatment

    b. HSE-MMP do not recommend treatment and notifies applicant of same.

3. HSE-MMP notifies the Office of the National Director for Acute Operations of their recommendation.

4. The Office of the National Director for Acute Operations notifies the prescribing consultant, the Hospital Group CEO and the HSE-MMP of the final decision.

If a patient is recommended and approved for reimbursement of OA, reimbursement will be supported for a maximum of one intravenous infusion, in line with the licensed dose as per SmPC. *See Section 2 for further details on Reimbursement criteria.*

1.4 Reimbursement price

The cost to the HSE of the presentation of OA, available under the Hospital Arrangement as of October 2021, is as follows:

Table 2: Cost* to the HSE of the presentation of OA available on the Hospital Arrangement

Strength and (pack size)	Cost to HSE
Zolgensma® 2 x 10^{13} vg/ml concentrate for solution for infusion	€1,945,000

ml: millilitre, vg: vector genomes *Price to wholesaler

A commercial in confidence arrangement is in place with the marketing authorisation holder to reduce the net acquisition cost of Zolgensma® 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 OA for the treatment of 5q SMA with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA type 1, **or** pre-symptomatic patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to three copies of the SMN2 gene under the Hospital Arrangement.

2.1 Prescribers

The prescribing of OA under the Hospital Arrangement will be 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 will be required to confirm a diagnosis of SMA at the time of application. Clinicians must provide evidence of a documented diagnosis based upon the following:

1. Confirmed diagnosis of 5q SMA with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA type 1, or
2. Confirmed diagnosis of pre-symptomatic 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene

2.2.1 Genetic testing

Confirmed genetic diagnosis of 5q SMA is a condition of reimbursement.

2.2.2 Antibody testing

An antibody test for AAV9 using an appropriately validated assay is required in advance of treatment; treatment is not recommended if the titre is greater than 1:50.

2.2.3 Age

There is limited experience in patients 2 years of age or older with body weight above 13.5 kg. The safety and efficacy of OA in these patients have not been established.

Confirmation of the age at onset of symptoms for patients with symptomatic SMA (5q SMA with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA type 1) is a condition of reimbursement.

2.3 Patient's clinical history

The license does not preclude the use of OA in patients who have been previously treated with other SMA therapies, nor does it preclude the subsequent use of other SMA therapies following OA treatment. Clinicians will be required to provide details pertaining to same at the time of application.

- Previous/current treatment with nusinersen/risdiplam?
- Whether treatment with nusinersen/risdiplam is expected to continue should treatment with OA be approved?
- Proposed duration of continued treatment with nusinersen/risdiplam?

Outcome measure scores e.g. Current Children's Hospital of Philadelphia Infant test of Neuromuscular Disorders (CHOP-INTEND), or other relevant outcome scores must be recorded at baseline to allow for assessment of efficacy of OA at follow-up. *See Section 3 for more detail.*

2.4 Patient's medical treatment

Clinicians will be required to provide details of the patient's medical treatment at the time of application.

2.5 Reimbursement exclusion criteria

Reimbursement will **not** be considered in patients:

- With any contraindication to treatment as set out in the SmPC for OA (Zolgensma®)
- With AAV9 titres of ≥ 1:50 following re-testing

3. Reimbursement criteria – Follow up

Following approval of a patient for reimbursement of OA under the Hospital 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 at least every six months to determine the effects of OA on disease progression. Outcome data, appropriate to the patient, should be submitted and sent by secure email to the MMP (mmp@hse.ie) 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,
- Length of event-free survival,
- Any changes to clinical history since initiation.

4. Reimbursement criteria – Medicines Management

Approved site(s) must ensure a local policy is in place to ensure appropriate medicines management, including protocols for thawing and administration of OA.

5. Prescribing of OA (Zolgensma® 2 x 10^{13} vg/ml solution for infusion)

Please refer to the SmPC for OA (Zolgensma®) for full prescribing information including monitoring and patient counselling requirements. Only approved prescriber(s) will be able to apply for OA reimbursement approval.

The following confirmations are required when prescribing OA:

- Confirmation that OA (Zolgensma®) 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's representative/guardian 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.