ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼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. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Zolgensma 2×10^{13} vector genomes/mL solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Onasemnogene abeparvovec is a gene therapy medicinal product that expresses the human survival motor neuron (SMN) protein. It is a non replicating recombinant adeno associated virus serotype 9 (AAV9) based vector containing the cDNA of the human SMN gene under the control of the cytomegalovirus enhancer/chicken-β-actin-hybrid promoter.

Onasemnogene abeparvovec is produced in human embryonic kidney cells by recombinant DNA technology.

2.2 Qualitative and quantitative composition

Each mL contains onasemnogene abeparvovec with a nominal concentration of 2×10^{13} vector genomes (vg). Vials will contain 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 (see sections 4.2 and 6.5).

Excipient with known effect
This medicinal product contains 0.2 mmol sodium per mL (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.
When thawed, it is a clear to slightly opaque, colourless to faint white solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zolgensma is indicated for 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.

4.2 Posology and method of administration

Treatment should be initiated and administered in clinical centres and supervised by a physician experienced in the management of patients with SMA.

Before administration of onasemnogene abeparvovec, baseline laboratory testing is required, including:

- AAV9 antibody testing using an appropriately validated assay
- liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin,
- platelet count, and
- troponin-I.

The need for close monitoring of liver function, platelet count and troponin-I after administration and the need for corticosteroid treatment are to be considered when establishing the timing of onasemnogene abeparvovec treatment (see section 4.4).

In case of acute or chronic uncontrolled active infections, treatment should be postponed until the infection has resolved or is controlled (see sub-sections 4.2 and 4.4 immunomodulatory regimen).

Posology

For single-dose intravenous infusion only.

Patients will receive a dose of nominal 1.1 x 10^{14} vg/kg onasemnogene abeparvovec. The total volume is determined by patient body weight.

Table 1 gives the recommended dosing for patients who weigh 2.6 to 21.0 kg.

Table 1 Recommended dosing based on patient body weight

Patient weight range (kg)	Dose (vg)	Total volume of dose [a] (mL)
2.6 – 3.0	3.3×10^{14}	16.5
3.1 – 3.5	3.9×10^{14}	19.3
3.6 – 4.0	4.4×10^{14}	22.0
4.1 – 4.5	5.0×10^{14}	24.8
4.6 – 5.0	5.5×10^{14}	27.5
5.1 – 5.5	6.1×10^{14}	30.3
5.6 – 6.0	6.6×10^{14}	33.0
6.1 – 6.5	7.2×10^{14}	35.8
6.6 – 7.0	7.7×10^{14}	38.5
7.1 – 7.5	8.3×10^{14}	41.3
7.6 – 8.0	8.8×10^{14}	44.0
8.1 – 8.5	9.4×10^{14}	46.8
8.6 – 9.0	9 .9 x 10^{14}	49.5
9.1 – 9.5	1.05 x 10^{15}	52.3
9.6 – 10.0	1.1 x 10^{15}	55.0
10.1 – 10.5	1.2 x 10^{15}	57.8
10.6 – 11.0	1.21 x 10^{15}	60.5
11.1 – 11.5	1.27 x 10^{15}	63.3
11.6 – 12.0	1.32 x 10^{15}	66.0
12.1 – 12.5	1.36 x 10^{15}	68.8
12.6 – 13.0	1.44 x 10^{15}	71.5
13.1 – 13.5	1.49 x 10^{15}	74.3

Patient weight range (kg)	Dose (vg)	Total volume of dose [a] (mL)
13.6 – 14.0	1.54×10^{15}	77.0
14.1 – 14.5	1.59×10^{15}	79.8
14.6 – 15.0	1.65×10^{15}	82.5
15.1 – 15.5	1.71×10^{15}	85.3
15.6 – 16.0	1.76×10^{15}	88.0
16.1 – 16.5	1.82×10^{15}	90.8
16.6 – 17.0	1.87×10^{15}	93.5
17.1 – 17.5	1.93×10^{15}	96.3
17.6 – 18.0	1.98×10^{15}	99.0
18.1 – 18.5	2.04×10^{15}	101.8
18.6 – 19.0	2.09×10^{15}	104.5
19.1 – 19.5	2.15×10^{15}	107.3
19.6 – 20.0	2.20×10^{15}	110.0
20.1 – 20.5	2.26×10^{15}	112.8
20.6 – 21.0	2.31×10^{15}	115.5

[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.

Immunomodulatory regimen

An immune response to the adeno associated viral vector serotype 9 (AAV9) capsid will occur after administration of onasemnogene abeparvovec (see section 4.4). This can lead to elevations in liver transaminases, elevations of troponin I, or decreased platelet counts (see sections 4.4 and 4.8). To dampen the immune response immunomodulation with corticosteroids is recommended. Where feasible, the patient's vaccination schedule should be adjusted to accommodate concomitant corticosteroid administration prior to and following onasemnogene abeparvovec infusion (see section 4.5).

Prior to initiation of the immunomodulatory regimen and prior to administration of onasemnogene abeparvovec, the patient must be checked for symptoms of active infectious disease of any nature.

Starting 24 hours prior to infusion of onasemnogene abeparvovec it is recommended to initiate an immunomodulatory regimen following the schedule below (Table 2). Deviations from these recommendations are at the discretion of the treating physician (see section 4.4).

Table 2 pre- and post-infusion immunomodulatory regimen

Pre-infusion	24 hours prior to onasemnogene abeparvovec	Prednisolone orally 1 mg/kg/day (or equivalent)
Post-infusion	30 days (including the day of administration of onasemnogene abeparvovec)	Prednisolone orally 1 mg/kg/day (or equivalent)
	followed by 28 days: *For patients with unremarkable findings (normal clinical exam, total bilirubin, and whose ALT and AST values are both below 2 × upper limit of normal (ULN) at the end of the 30 days period:* **or** *For patients with liver function abnormalities at the end of the 30 days period: continuing until the AST and ALT values are below 2 × ULN and all other assessments return to normal range, followed by tapering over 28 days.*	 Tapering of prednisolone (or equivalent), e.g. 2 weeks at 0.5 mg/kg/day and then 2 weeks at 0.25 mg/kg/day oral prednisolone Systemic corticosteroids (equivalent to oral prednisolone 1 mg/kg/day)

	Liver transaminases should be monitored for at least 3 months following onasemnogene abeparvovec infusion (see section 4.4)

Consult expert(s) if patients do not respond adequately to the equivalent of 1 mg/kg/day oral prednisolone.

If another corticosteroid is used by the physician in place of prednisolone, similar considerations and approach to taper the dose after 30 days should be taken as appropriate.

Special populations

Renal impairment
The safety and efficacy of onasemnogene abeparvovec have not been established in patients with renal impairment and onasemnogene abeparvovec therapy should be carefully considered. A dose adjustment should not be considered.

Hepatic impairment
Onasemnogene abeparvovec has not been studied in patients with hepatic impairment. Onasemnogene abeparvovec should not be infused unless elevated bilirubin is associated with neonatal jaundice. Onasemnogene abeparvovec therapy should be carefully considered in patients with hepatic impairment (see sections 4.4 and 4.8). A dose adjustment should not be considered.

0SMN1/1SMN2 genotype
No dose adjustment should be considered in patients with a bi-allelic mutation of the SMN1 gene and only one copy of SMN2 (see section 5.1).

Anti-AAV9 antibodies
No dose adjustment should be considered in patients with baseline anti-AAV9 antibody titres above 1:50 (see section 4.4).

Paediatric population
The safety and efficacy of onasemnogene abeparvovec in premature neonates before reaching full-term gestational age have not been established. No data are available. Administration of onasemnogene abeparvovec should be carefully considered because concomitant treatment with corticosteroids may adversely affect neurological development.

There is limited experience in patients 2 years of age and older or with body weight above 13.5 kg. The safety and efficacy of onasemnogene abeparvovec in these patients have not been established. Currently available data are described in section 5.1. A dose adjustment should not be considered (see Table 1).

Method of administration

For intravenous use.

Onasemnogene abeparvovec is administered as a single-dose intravenous infusion. It should be administered with the syringe pump administered as a single intravenous infusion with a slow infusion of approximately 60 minutes. It must not be administered as an intravenous push or bolus.

Insertion of a secondary (‘back-up’) catheter is recommended in case of blockage in the primary catheter. Following completion of infusion, the line should be flushed with saline.

For instructions on dilution of the product before administration, see section 6.6

Precautions to be taken before handling or administering the medicinal product
This medicinal product contains a genetically-modified organism. Personal protective equipment (to include laboratory coat, safety glasses and gloves) should be worn while preparing or administering onasemnogene abeparvovec (see sections 6.6). For instructions on the preparation, handling,

accidental exposure to and disposal of the medicinal product, including proper handling of bodily waste see 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Pre-existing immunity against AAV9
Anti-AAV9 antibody formation can take place after natural exposure. There have been several studies on the prevalence of AAV9 antibodies in the general population that show low rates of prior exposure to AAV9 in the paediatric population. Patients should be tested for the presence of AAV9 antibodies prior to infusion with onasemnogene abeparvovec. Retesting may be performed if AAV9 antibody titres are reported as above 1:50. It is not yet known whether or under what conditions onasemnogene abeparvovec can be safely and effectively administered in the presence of anti-AAV9 antibodies above 1:50 (see sections 4.2 and 5.1).

Advanced SMA
Since SMA results in progressive and non-reversible damage to motor neurons, the benefit of onasemnogene abeparvovec in symptomatic patients depends on the degree of disease burden at the time of treatment, with earlier treatment resulting in potential higher benefit. While advanced symptomatic SMA patients will not achieve the same gross motor development as unaffected healthy peers they may clinically benefit from gene replacement therapy, dependent on the advancement of disease at the time of treatment (see section 5.1).

The treating physician should consider that the benefit is seriously reduced in patients with profound muscle weakness and respiratory failure, patients on permanent ventilation, and patients not able to swallow.

The benefit/risk profile of onasemnogene abeparvovec in patients with advanced SMA, kept alive through permanent ventilation and without the ability to thrive is not established.

Immunogenicity
An immune response to the adeno associated viral vector serotype 9 (AAV9) capsid will occur after infusion of onasemnogene abeparvovec, including antibody formation against the AAV9 capsid despite the immunomodulatory regimen recommended in section 4.2, and T-cell mediated immune response.

Systemic immune response, including immune-mediated hepatotoxicity, has been reported in the onasemnogene abeparvovec clinical program and may require adjustment of immunomodulatory regimen including longer duration or increased dose. Refer to section 4.2 for immunomodulatory regimen, to the sub-sections hepatic injury and immunomodulatory regimen below for details.

Hepatic injury

- Administration of AAV vector may result in transaminase elevations, which may be serious.
- Acute serious liver injury has occurred (see section 4.8).
- Patients with pre-existing liver impairment or acute hepatic viral infection may be at higher risk of liver injury.

- Prior to infusion, liver function of all patients should be assessed by clinical examination and laboratory testing (e.g., hepatic aminotransferases AST and ALT, and total bilirubin (see section 4.2)).
- In order to mitigate potential transaminase elevations, a systemic corticosteroid should be administered to all patients before and after onasemnogene abeparvovec infusion (see section 4.2).
- Liver function should be monitored for at least 3 months after infusion.
- The risks and benefits of infusion with onasemnogene abeparvovec in pre-existent hepatic impairment should be weighed carefully against the risks of not treating the patient.

AST/ALT/bilirubin should be assessed weekly for 30 days and every two weeks for an additional 60 days post administration of onasemnogene abeparvovec through the end of the corticosteroid taper, or longer if needed. Tapering of prednisolone should not be considered until AST/ALT are less than 2x ULN.

Thrombocytopenia
Transient decreases in platelet counts, some of which met the criteria for thrombocytopenia, were observed in onasemnogene abeparvovec clinical trials. In most cases, the lowest platelet value occurred the first week following onasemnogene abeparvovec infusion. Platelet counts should be obtained before onasemnogene abeparvovec infusion and monitored on a regular basis afterwards, weekly for the first month and every other week for the second and third months until platelet counts return to baseline.

Elevated troponin-I
Increases in cardiac troponin-I levels following infusion with onasemnogene abeparvovec were observed. Elevated troponin-I levels found in some patients may indicate potential myocardial tissue injury. Based on these findings and the observed cardiac toxicity in mice, troponin-I levels should be obtained before onasemnogene abeparvovec infusion and monitored for at least 3 months following onasemnogene abeparvovec infusion or until levels return to within normal reference range for SMA patients. Consider consultation with a cardiac expert as needed.

Immunomodulatory regimen
Immunomodulatory treatment should not be initiated concurrently to active infections, either acute (such as acute respiratory infections or acute hepatitis) or uncontrolled chronic (such as chronic active hepatitis B) (see sections 4.2 and 4.4).

The immunomodulatory regimen (see section 4.2) might also impact the immune response to concurrent (respiratory) infections, potentially resulting in more severe clinical courses of the concurrent infection. Added caution is advised regarding the timing of onasemnogene abeparvovec dosing in the presence of prodrome or resolving (viral) illness. Increased vigilance in the diagnosis and active management of (viral) respiratory infection is recommended. Seasonal prophylactic treatments, that prevent respiratory syncytial virus (RSV) infections, are recommended and should be up to date. Where feasible, the patient's vaccination schedule should be adjusted to accommodate concomitant corticosteroid administration prior to and following onasemnogene abeparvovec infusion (see section 4.5).

The treating physician should be aware of the possibility of adrenal insufficiency related to longer duration of treatment with corticosteroids which might impact the proposed immunomodulatory regimen.

Shedding
Temporary onasemnogene abeparvovec shedding occurs, primarily through bodily waste. Caregivers and patient families should be advised on the following instructions for the proper handling of patient stools:
- good hand-hygiene is required when coming into direct contact with patient bodily waste for a minimum of 1 month after onasemnogene abeparvovec treatment.
- Disposable diapers can be sealed in double plastic bags and disposed of in household waste.

Sodium content
This medicinal product contains 4.6 mg sodium per mL, equivalent to 0.23% of the WHO recommended maximum daily intake of 2 g sodium for an adult. Each 5.5 mL vial contains 25.3 mg sodium, and each 8.3 mL vial contains 38.2 mg sodium.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Experience with use of onasemnogene abeparvovec in patients receiving hepatotoxic medication or using hepatotoxic substances is limited. Safety of onasemnogene abeparvovec in these patients have not been established.

Experience with use of concomittant 5q SMA targeting agents is limited.

Vaccinations
Where feasible, the patient's vaccination schedule should be adjusted to accommodate concomitant corticosteroid administration prior to and following onasemnogene abeparvovec infusion (see sections 4.2 and 4.4). Seasonal RSV prophylaxis is recommended (see section 4.4). Live vaccines, such as MMR and varicella, should not be administered to patients on an immunosuppressive steroid dose (i.e., ≥ 2 weeks of daily receipt of 20 mg or 2 mg/kg body weight of prednisolone or equivalent).

4.6 Fertility, pregnancy and lactation

Human data on use during pregnancy or lactation are not available and animal fertility or reproduction studies have not been performed.

4.7 Effects on ability to drive and use machines

Onasemnogene abeparvovec has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most frequently reported adverse reaction following administration was transient hepatic transaminase increase (12.4%) and vomiting (8.2%), see section 4.4.

Tabulated list of adverse reactions
The adverse reactions identified with onasemnogene abeparvovec in all patients treated with intravenous infusion with a causal association to treatment are presented in Table 3. Adverse reactions are classified according to MedDRA system organ classification and frequency. Frequency categories are derived according to the following conventions: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3 Tabulated list of adverse reactions to onasemnogene abeparvovec

Adverse Reactions by MedDRA SOC/PT and Frequency	
Blood and lymphatic system disorders	
Common	Thrombocytopenia
Gastrointestinal disorders	
Common	Vomiting
General disorders and administration site conditions	
Common	Pyrexia
Investigations	
Very Common	Transaminases increased

Adverse Reactions by MedDRA SOC/PT and Frequency	
Common	Aspartate aminotransferase increased, alanine aminotransferase increased, troponin-I increased

Description of selected adverse reactions

Hepatobiliary disorders
Elevated transaminases greater than 2 times ULN were reported in up to 12% of patients treated at the recommended dose and were considered study-drug related. Two patients had AST and ALT elevations of > 20 × ULN (one of these patients was experiencing a viral infection). These patients were clinically asymptomatic, did not exhibit jaundice or a clinically significant elevation of bilirubin and did not meet Hy's Law criteria. Serum transaminase elevations resolved with prednisolone treatment (see sections 4.2 and 4.4), and patients recovered without clinical sequelae.

Outside of clinical trials, a case of acute serious liver injury was reported with onasemnogene abeparvovec where the patient was continuing treatment with nusinersen and had AST and ALT elevations of > 3 × ULN before treatment with onasemnogene abeparvovec. The patient recovered with additional steroid therapy.

Transient thrombocytopenia
Transient decreases from baseline in mean platelet counts (4.1%) were observed at multiple time points post-dose and normally resolved within two weeks. Decreases in platelet counts were more prominent during the first week of treatment. No patients had clinical symptoms associated with decreased platelets. (see section 4.4).

Increases of troponin-I levels
Increases in cardiac troponin-I levels (3.1%) up to 0.2 mcg/L following onasemnogene abeparvovec infusion were observed. In the clinical trial program, there were no clinically apparent cardiac findings observed following administration of onasemnogene abeparvovec (see section 4.4).

Immunogenicity
Pre- and post-gene therapy titres of anti-AAV9 antibodies were measured in the clinical studies (see section 4.4). All patients that received onasemnogene abeparvovec had anti-AAV9 titres at or below 1:50 before treatment. Mean increases from baseline in AAV9 titre were observed in all patients at all but 1 time point for antibody titre levels to AAV9 peptide, reflecting normal response to non-self viral antigen. Some patients experienced AAV9 titres exceeding the level of quantification, however most of these patients did not have potentially clinically significant adverse reactions. Thus, no relationship has been established between high anti-AAV9 antibody titres and the potential for adverse reactions or efficacy parameters.

In the AVXS-101-CL-101 clinical study, 16 patients were screened for anti-AAV9 antibody titre: 13 had titres less than 1:50 and were enrolled in the study; three patients had titres greater than 1:50, two of whom were retested following cessation of breast-feeding and their titres were measured at less than 1:50 and both were enrolled in the study. There is no information on whether breastfeeding should be restricted in mothers who may be seropositive for anti-AAV9 antibodies. Patients all had less than or equal to 1:50 AAV9 antibody titre prior to treatment with onasemnogene abeparvovec and subsequently demonstrated an expected increase in anti-AAV9 antibody titres to at least 1:102,400 and up to greater than 1:819,200.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. In addition, the observed incidence of antibody (including neutralising antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medicinal products and underlying disease.

No onasemnogene abeparvovec-treated patient demonstrated an immune response to the transgene.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No data from clinical studies are available regarding overdose of onasemnogene abeparvovec. Adjustment of the dose of prednisolone, close clinical observation and monitoring of laboratory parameters (including clinical chemistry and haematology) for systemic immune response are recommended (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other drugs for disorders of the musculo-skeletal system, ATC code: M09AX09

Mechanism of action
Onasemnogene abeparvovec 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 tranduced motor neurons.

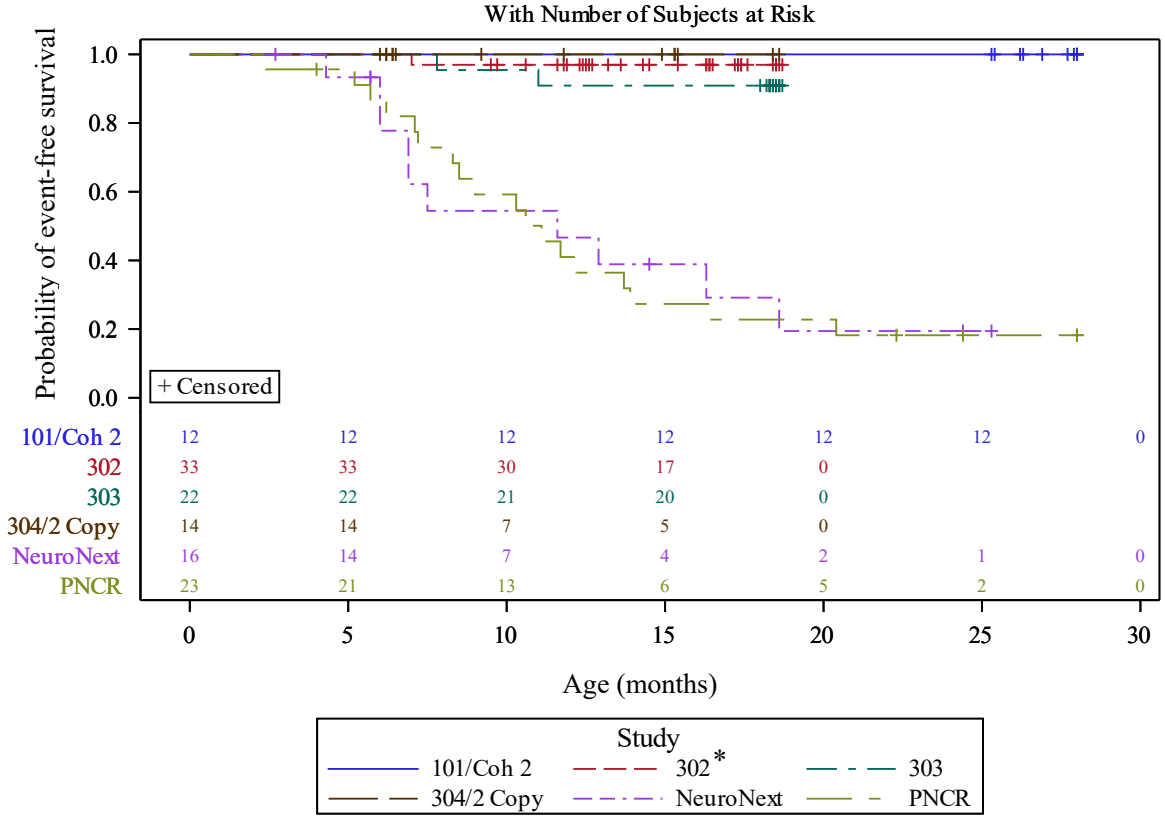
Onasemnogene abeparvovec is a non-replicating recombinant AAV vector that utilizes AAV9 capsid to deliver a stable, fully functional human SMN transgene. The ability of the AAV9 capsid to cross the blood brain barrier and transduce motor neurons has been demonstrated. The *SMN1* gene present in onasemnogene abeparvovec is designed to reside as episomal DNA in the nucleus of transduced cells and is expected to be stably expressed for an extended period of time in post-mitotic cells. The AAV9 virus is not known to cause disease in humans. The transgene is introduced to target cells as a self-complementary double-stranded molecule. Expression of the transgene is driven by a constitutive promoter (cytomegalovirus enhanced chicken β-actin hybrid), which results in continuous and sustained SMN protein expression. Proof of the mechanism of action has been supported by non-clinical studies and by human biodistribution data.

Clinical efficacy and safety

AVXS-101-CL-303 Phase 3 Study in Patients with Type 1 SMA

AVXS-101-CL-303 (Study 303) is a Phase 3 open-label, single-arm, single-dose study of intravenous administration of onasemnogene abeparvovec at the therapeutic dose (1.1×10^{14} vg/kg). Twenty two patients were enrolled with Type 1 SMA and 2 copies of *SMN2*. Patient ages at administration ranged from 0.5 to 5.9 months. Of the 22 enrolled patients, three patients discontinued the study of which two patients had an event (death or permanent ventilation) leading to 90.9% (95% CI: 79.7%, 100.0%) event-free survival (alive without permanent ventilation) at 14 months of age, see Figure 1.

Figure 1 Time (days) to death or permanent ventilation pooled from onasemnogene abeparvovec IV studies (CL-101, CL-302, CL-303, CL-304-2 copy cohort)



PNCR = Pediatric Neuromuscular Clinical Research natural history cohort
NeuroNext = Network for Excellence in Neuroscience Clinical Trials natural history cohort
* AVXS-101-CL-302 is an ongoing Phase 3 multicenter, open-label, single-arm, single-dose study of AVXS-101 (gene replacement therapy) in patients with SMA Type 1 with 1 or 2 copies of the *SMN2* gene similar to study AVXS-101-CL-303. The average age of the patients in the study at time of the 31 December 2019 data cutoff is 10.62 months (range 1.8 to 15.4 months).

For the 14 patients in Study CL-303 that achieved the milestone of independent sitting for at least 30 seconds, the median age when this milestone was first demonstrated was 12.5 months (range 9.2 to 18.6 months. Thirteen patients confirmed the milestone of independent sitting for at least 30 seconds at the 18 month visit (co-primary endpoint, $p<0.0001$). One patient achieved the milestone of sitting independently for 30 seconds at 16 months of age, but this milestone was not confirmed at the Month 18 visit. The video-confirmed developmental milestones for patients in Study CL-303 are summarised in Table 4. Three patients did not achieve any motor milestones (13.6%) and six patients (27.2%) achieved head control as the maximum motor milestone before the 18 months of age final study visit.

Table 4 Median time to video document achievement of motor milestones Study 303

Video documented milestone	Number of patients achieving milestone n/N (%)	Median age to the milestone achievement (Months)	95% Confidence interval
Head control	17/20 (85)	6.8	(4.77, 7.17)
Rolls from back to sides	13/22 (59)	11.5	(7.77, 14.53)
Sits without support for 30 seconds (Bayley)	14/22 (64)	12.5	(10.17, 15.20)

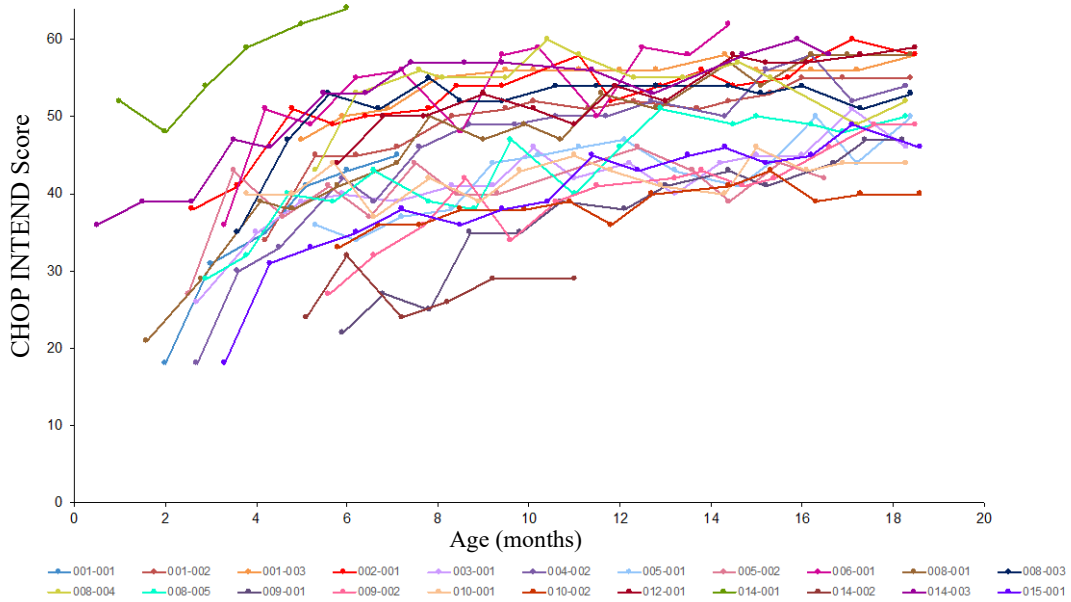
Sitting without support for at least 10 seconds (WHO)	14/22 (64)	13.9	(11.00, 16.17)

*2 patients were reported to have Head Control by clinician assessment at baseline.

One patient (4.5%) could also walk with assistance at 12.9 months. Based on the natural history of the disease, patients who met the study entry criteria would not be expected to attain the ability to sit without support.

Motor function improvements were also observed as measured by the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND), see Figure 2. Twenty-one patients (95.5%) achieved a CHOP-INTEND score ≥ 40, 14 (64%) had achieved a CHOP-INTEND score ≥ 50, and 5 patients (23%) had achieved a CHOP-INTEND score ≥ 60. Patients with untreated SMA Type 1 almost never achieve a CHOP-INTEND score ≥ 40. Motor milestone achievement was observed in some patients despite plateauing of CHOP-INTEND. No clear correlation was observed between CHOP-INTEND scores and motor milestone achievement.

Figure 2 CHOP-INTEND Motor Function Scores Study 303



AVXS-101-CL-101 Phase 1 Study in Patients with Type 1 SMA

The results seen in Study 303 are supported by study AVXS-101-CL-101 (Phase 1 study in Type 1 SMA, Study 101) in which onasemnogene abeparvovec was administered as a single intravenous infusion in 12 patients from 2.6 kg to 8.5 kg (0.9 to 7.9 months of age). At 14 months of age, all treated patients were event free; i.e. survived without permanent ventilation, compared to 25% in the natural history cohort. At the end of the study (24 months post dose), all treated patients were event free, compared to less than 8% in the natural history, see Figure 1.

At 24 months of follow up post dose, 10 out of 12 patients were able to sit without support for ≥ 10 seconds, 9 patients were able to sit without support for ≥ 30 seconds and 2 patients were able to stand and walk without assistance. One out of 12 patients did not achieve head control as the maximum motor milestone before the age of 24 months. Ten of 12 patients from Study CL-101 who received the proposed therapeutic dose of onasemnogene abeparvovec continue to be followed in a long-term study (for up to 5.7 years after dosing) and all have either maintained all previously attained milestones or even gained new milestones including such as sitting with support, stand with assistance and walk alone. Four of the 10 patients received concomitant nusinersen treatment at some point during the long-term study. Maintenance of efficacy and achievement of milestones can therefore not

be solely attributed to onasemnogene abeparvovec in all patients. The milestone of stand with assistance was newly acquired by two patients who were not receiving nusinersen.

AVXS-101-CL-304 Phase 3 Study in Patients with pre-symptomatic SMA
Study CL-304 is an ongoing, global, Phase 3, open-label, single-arm, single-dose, multicenter study of IV AVXS-101 in pre-symptomatic newborn patients up to 6 weeks of age with 2 (cohort 1, n=14) or 3 (cohort 2, n=15) copies of SMN2.

Cohort 1
At the time of the last study visit prior to 31 December 2019, treated patients with 2 copies of SMN2 were between 6 months and 18.6 months of age and had been in the study for an average of 10.5 months (range: 5.1 to 18.0 months). All patients were alive and free of permanent ventilation.

Eight patients achieved independent sitting for at least 30 seconds, at ages ranging from 6.4 to 11.8 months, with 7 of these 8 (87.5%) achieving independent sitting prior to the 9.2 months of age, the 99th percentile for development of this milestone. Four patients achieved the milestone of walking alone (28.6%). Twelve (12) patients (85.7%) have achieved CHOP-INTEND scores ≥ 60 as of the 31 December 2019 data cutoff.

Cohort 2
At the time of the last study visit prior to 31 December 2019, treated patients with 3 copies of SMN2 were between 3.3 and 15.1 months of age and had been in the study for an average of 8.74 months (range: 2 to 13.9 months). All patients were alive and free of permanent ventilation. Ten of 15 patients were able to sit without support for at least 30 seconds, 4 patients were able to stand alone without support for at least 3 seconds, and 2 patients walk at least five steps independently.
The follow up duration is too short to assess the development of patients treated with AVXS-101 treatment compared to the natural history of patients with 3 SMN2 copies, who have a heterogeneous clinical presentation. Therefore, no definitive conclusions about the benefit in this patient population can be drawn at this moment.

Onasemnogene abeparvovec has not been studied in patients with a bi-allelic mutation of the *SMN1* gene and only one copy of *SMN2* in clinical trials.

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

The European Medicines Agency has deferred the obligation to submit the results of studies with onasemnogene abeparvovec in one or more subsets of the paediatric population in Spinal Muscular Atrophy for the granted indication (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Onasemnogene abeparvovec vector shedding studies, which assess the amount of vector eliminated from the body through saliva, urine and faeces were performed.

Onasemnogene abeparvovec was detectable in shedding samples post-infusion. Clearance of onasemnogene abeparvovec was primarily via faeces and the majority is cleared within 30 days after dose administration. Onasemnogene abeparvovec concentrations in urine and saliva were 0.1% to 0.01% of initial concentration in the body at day 1 post infusion and dropped thereafter.

Biodistribution was evaluated in two patients who died 5.7 months and 1.7 months, respectively, after infusion of onasemnogene abeparvovec at the dose of 1.1×10^{14} vg/kg. Both cases showed that the highest levels of vector DNA were found in the liver. Vector DNA was also detected in the spleen, heart, pancreas, inguinal lymph node, skeletal muscles, peripheral nerves, kidney, lung, intestines, spinal cord, brain, and thymus. Immunostaining for SMN protein showed generalized SMN expression

in spinal motor neurons, neuronal and glial cells of the brain, and in the heart, liver, skeletal muscles, and other tissues evaluated.

5.3 Preclinical safety data

Following intravenous administration in neonatal mice, vector and transgene were widely distributed with the highest expression generally observed in heart and liver, and substantial expression in the brain and spinal cord. In pivotal 3 month mouse toxicology studies, the main target organs of toxicity identified were the heart and liver. Onasemnogene abeparvovec-related findings in the ventricles of the heart were comprised of dose-related inflammation, oedema and fibrosis. In the atria of the heart, inflammation, thrombosis, myocardial degeneration/necrosis and fibroplasia were observed. Liver findings were comprised of hepatocellular hypertrophy, Kupffer cell activation, and scattered hepatocellular necrosis. A No Adverse Effect Level (NoAEL) was not identified for onasemnogene abeparvovec in the mouse as ventricular myocardial inflammation/oedema/fibrosis and atrial inflammation were observed at the lowest dose tested (1.5×10^{14} vg/kg). This dose is regarded the Maximum Tolerated Dose and approximately 1.4 fold the recommended clinical dose. Onasemnogene abeparvovec-related mortality was, in the majority of mice, associated with atrial thrombosis, and observed at 2.4×10^{14} vg/kg. The cause of the mortality in the rest of the animals was undetermined, although microscopic degeneration/regeneration in the hearts of these animals was found.

Genotoxicity, carcinogenicity and reproduction toxicity studies have not been conducted with onasemnogene abeparvovec.

In a toxicology study conducted in young adult non-human primates, administration of a single dose of $3x10^{13}$ vg/NHP (median dose $1.08x10^{13}$ vg/kg) onasemnogene abeparvovec intrathecally with Trendelenburg position, without corticosteroid treatment, resulted in minimal to marked mononuclear cell inflammation (primarily lymphocytes) in some dorsal root ganglia from all examined spinal cord levels, with neuronal satellitosis, neuronal necrosis, or complete neuronal loss with rare mineralization. The clinical relevance of this finding is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tromethamine
Magnesium chloride
Sodium chloride
Poloxamer 188
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product should not be mixed with other medicinal products.

6.3 Shelf life

1 year

After thawing
Once thawed, the medicinal product should not be re-frozen and may be stored refrigerated at 2°C to 8°C in the original carton for 14 days.

Once the dose volume is drawn into the syringe it must be infused within 8 hours. Discard the vector containing syringe if not infused within the 8 hour timeframe.

6.4 Special precautions for storage

Store and transport frozen (≤ -60°C).
Store in a refrigerator (2 -8°C) immediately upon receipt.
Store in the original carton.
For storage conditions after thawing of the medicinal product, see section 6.3.
The date of receipt should be marked on the original carton before the product is stored in the refrigerator.

6.5 Nature and contents of container

Onasemnogene abeparvovec 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.

The dose of onasemnogene abeparvovec and exact number of vials required for each patient is calculated according to the patient's weight (see section 4.2 and Table 5 below).

Table 5 Carton/kit configurations

Patient weight (kg)	5.5 mL vial[a]	8.3 mL vial[b]	Total vials per carton
2.6 – 3.0	0	2	2
3.1 – 3.5	2	1	3
3.6 – 4.0	1	2	3
4.1 – 4.5	0	3	3
4.6 – 5.0	2	2	4
5.1 – 5.5	1	3	4
5.6 – 6.0	0	4	4
6.1 – 6.5	2	3	5
6.6 – 7.0	1	4	5
7.1 – 7.5	0	5	5
7.6 – 8.0	2	4	6
8.1 – 8.5	1	5	6
8.6 – 9.0	0	6	6
9.1 – 9.5	2	5	7
9.6 – 10.0	1	6	7
10.1 – 10.5	0	7	7
10.6 – 11.0	2	6	8
11.1 – 11.5	1	7	8
11.6 – 12.0	0	8	8
12.1 – 12.5	2	7	9
12.6 – 13.0	1	8	9
13.1 – 13.5	0	9	9
13.6 – 14.0	2	8	10
14.1 – 14.5	1	9	10
14.6 – 15.0	0	10	10
15.1 – 15.5	2	9	11
15.6 – 16.0	1	10	11
16.1 – 16.5	0	11	11

Patient weight (kg)	5.5 mL vial[a]	8.3 mL vial[b]	Total vials per carton
16.6 – 17.0	2	10	12
17.1 – 17.5	1	11	12
17.6 – 18.0	0	12	12
18.1 – 18.5	2	11	13
18.6 – 19.0	1	12	13
19.1 – 19.5	0	13	13
19.6 – 20.0	2	12	14
20.1 – 20.5	1	13	14
20.6 – 21.0	0	14	14

[a] Vial nominal concentration is 2 × 1013 vg/mL and contains an extractable volume of not less than 5.5 mL.

[b] Vial contains nominal concentration is 2 × 1013 vg/mL and an extractable volume of not less than 8.3 mL.

6.6 Special precautions for disposal and other handling

This medicinal product contains genetically-modified organisms. Appropriate precautions for the handling, disposal or accidental exposure of onasemnogene abeparvovec should be followed:

- The onasemnogene abeparvovec syringe should be handled aseptically under sterile conditions.
- Personal protective equipment (to include gloves, safety goggles, laboratory coat and sleeves) should be worn while handling or administering onasemnogene abeparvovec. Personnel should not work with onasemnogene abeparvovec if skin is cut or scratched.
- All spills of onasemnogene abeparvovec must be wiped with absorbent gauze pad and the spill area must be disinfected using a bleach solution followed by alcohol wipes. All clean up materials must be double bagged and disposed of per local guidelines for handling of biological waste.
- All materials that may have come in contact with onasemnogene abeparvovec (e.g. vial, all materials used for injection, including sterile drapes and needles) must be disposed of in accordance with local guidelines on handling of biological waste.
- Accidental exposure to onasemnogene abeparvovec must be avoided. In the event of exposure to skin, the affected area must be thoroughly cleaned with soap and water for at least 15 minutes. In the event of exposure to eyes, the affected area must be thoroughly flushed with water for at least 15 minutes.

<u>Receipt and thawing vials</u>

- Vials will be transported frozen (≤-60ºC). Upon receipt vials should be refrigerated at 2°C to 8°C immediately, and in the original carton. Onasemnogene abeparvovec therapy should be initiated within 14 days of receipt of vials.
- Vials must be thawed before use. Do not use onasemnogene abeparvovec unless thawed.
- For packaging configurations containing up to 9 vials, product will be thawed after approximately 12 hours in the refrigerator. For packaging configurations containing up to 14 vials, product will be thawed after approximately 16 hours in the refrigerator. Alternatively, and for immediate use, thawing may be performed at room temperature.
- For packaging configurations containing up to 9 vials, thawing will occur from frozen state after approximately 4 hours at room temperature (20°C to 25°C). For packaging configurations containing up to 14 vials, thawing will occur from frozen state after approximately 6 hours at room temperature (20°C to 25°C)
- Before drawing the dose volume into the syringe, gently swirl the thawed product. Do NOT shake.
- Do not use this medicine if you notice any particles or discolouration once the frozen product has thawed and prior to administration.
- Once thawed, the medicinal product should not be re-frozen.

- After thawing, onasemnogene abeparvovec should be given as soon as possible. Once the dose volume is drawn into the syringe it must be infused within 8 hours. Discard the vector-containing syringe if not infused within the 8-hour timeframe.

Administration of onasemnogene abeparvovec to the patient
- To administer onasemnogene abeparvovec, draw the entire dose volume into the syringe. Remove any air in the syringe and prepare the infusion bag before intravenous infusion through a venous catheter.

Any unused medicinal product or waste material should be disposed of in accordance with local guidelines on handling of biological waste.

Temporary onasemnogene abeparvovec shedding may occur, primarily through bodily waste. Caregivers and patient families should be advised on the following instructions for the proper handling of patient bodily fluids and waste:
- Good hand-hygiene (wearing protective gloves and washing hands thoroughly afterwards with soap and warm running water, or an alcohol-based hand sanitiser) is required when coming into direct contact with patient bodily fluids and waste for a minimum of 1 month after onasemnogene abeparvovec treatment.
- Disposable diapers should be sealed in double plastic bags and can be disposed of in household waste.

7. MARKETING AUTHORISATION HOLDER

AveXis EU Limited
Block B, The Crescent Building
Northwood, Santry
Dublin 9
D09 C6X8
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1443/001
EU/1/20/1443/002
EU/1/20/1443/003
EU/1/20/1443/004
EU/1/20/1443/005
EU/1/20/1443/006
EU/1/20/1443/007
EU/1/20/1443/008
EU/1/20/1443/009
EU/1/20/1443/010
EU/1/20/1443/011
EU/1/20/1443/012
EU/1/20/1443/013
EU/1/20/1443/014
EU/1/20/1443/015
EU/1/20/1443/016
EU/1/20/1443/017
EU/1/20/1443/018
EU/1/20/1443/019
EU/1/20/1443/020
EU/1/20/1443/021
EU/1/20/1443/022

EU/1/20/1443/023
EU/1/20/1443/024
EU/1/20/1443/025
EU/1/20/1443/026
EU/1/20/1443/027
EU/1/20/1443/028
EU/1/20/1443/029
EU/1/20/1443/030
EU/1/20/1443/031
EU/1/20/1443/032
EU/1/20/1443/033
EU/1/20/1443/034
EU/1/20/1443/035
EU/1/20/1443/036
EU/1/20/1443/037

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)
AveXis, Inc.
1940 USG Drive
Libertyville
IL 60048
United States

Name and address of the manufacturer(s) responsible for batch release
Almac Pharma Services (Ireland) Limited
Finnabair Industrial Estate
Dundalk
Co. Louth
A91 P9KD
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Non-interventional post-authorisation efficacy study (PAES): In order to further characterise and contextualise the outcomes of patients with a diagnosis of SMA, including long-term safety and efficacy of Zolgensma, the MAH should conduct and submit the results of a prospective observational registry AVXS-101-RG-001 according to an agreed protocol.	Interim reports to be submitted with annual renewal. Final study report 2038.
The applicant should perform a further evaluation of the finished product specifications when primary and key secondary endpoint data from additional patients with 2 copies of SMN2 are available (i.e. completion of CL-302 and CL-304 cohort 1). Based on this evaluation, it should be determined whether tightening of the release specification limits is needed to improve consistency of the batches and ensure optimal clinical outcome.	Dec 2021 with completion of Study CL-302 and Cohort 1 in Study CL-304

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14a(4) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
Post-authorisation efficacy study (PAES): In order to confirm the efficacy and safety and tolerability of a single dose of Zolgensma in patients younger than 6 months of age with Spinal Muscular Atrophy Type 1 with One or Two *SMN2* Copies the MAH should submit final data on Study AVXS-101-CL-303	Final results: at first annual renewal
Post-authorisation efficacy study (PAES): In order to confirm the efficacy and safety and tolerability of a single dose of Zolgensma in patients younger than 6 months of age with Spinal Muscular Atrophy Type 1 with One or Two *SMN2* Copies the MAH should submit interim and final data on Study AVXS-101-CL-302	Interim results: at each annual renewal Final results: Aug 2021
Post-authorisation efficacy study (PAES): In order to confirm the efficacy and safety and tolerability of a single dose of Zolgensma in genetically diagnosed and pre-symptomatic patients equal or younger than 6 weeks of age at time of treatment with SMA with bi-allelic deletion of *SMN1* with 2 or 3 copies of *SMN2*, the MAH should submit interim and final data on Study AVXS-101-CL-304	Interim results: at each annual renewal Final results: Aug 2026

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – GENERIC LABELLING

1. NAME OF THE MEDICINAL PRODUCT

Zolgensma 2 x 10^{13} vector genomes/mL solution for infusion
onasemnogene abeparvovec

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains onasemnogene abeparvovec equivalent to 2 x 10^{13} vector genomes/mL.

3. LIST OF EXCIPIENTS

Also contains tromethamine, magnesium chloride, sodium chloride, poloxamer 188, hydrochloric acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
8.3 mL vial x 2
5.5 mL vial x 2, 8.3 mL vial x 1
5.5 mL vial x 1, 8.3 mL vial x 2
8.3 mL vial x 3
5.5 mL vial x 2, 8.3 mL vial x 2
5.5 mL vial x 1, 8.3 mL vial x 3
8.3 mL vial x 4
5.5 mL vial x 2, 8.3 mL vial x 3
5.5 mL vial x 1, 8.3 mL vial x 4
8.3 mL vial x 5
5.5 mL vial x 2, 8.3 mL vial x 4
5.5 mL vial x 1, 8.3 mL vial x 5
8.3 mL vial x 6
5.5 mL vial x 2, 8.3 mL vial x 5
5.5 mL vial x 1, 8.3 mL vial x 6
8.3 mL vial x 7
5.5 mL vial x 2, 8.3 mL vial x 6
5.5 mL vial x 1, 8.3 mL vial x 7
8.3 mL vial x 8
5.5 mL vial x 2, 8.3 mL vial x 7
5.5 mL vial x 1, 8.3 mL vial x 8
8.3 mL vial x 9
5.5 mL vial x 2, 8.3 mL vial x 8
5.5 mL vial x 1, 8.3 mL vial x 9
8.3 mL vial x 10
5.5 mL vial x 2, 8.3 mL vial x 9
5.5 mL vial x 1, 8.3 mL vial x 10
8.3 mL vial x 11
5.5 mL vial x 2, 8.3 mL vial x 10
5.5 mL vial x 1, 8.3 mL vial x 11
8.3 mL vial x 12

5.5 mL vial x 2, 8.3 mL vial x 11
5.5 mL vial x 1, 8.3 mL vial x 12
8.3 mL vial x 13
5.5 mL vial x 2, 8.3 mL vial x 12
5.5 mL vial x 1, 8.3 mL vial x 13
8.3 mL vial x 14

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use.
Single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Must use within 14 days of receipt.

9. SPECIAL STORAGE CONDITIONS

Store and transport frozen at ≤-60°C.
Store in a refrigerator 2-8°C immediately upon receipt.
Store in the original carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains genetically-modified organisms.
Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of biological waste.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AveXis EU Limited
Block B, The Crescent Building
Northwood, Santry
Dublin 9
D09 C6X8
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1443/001 – 8.3 mL vial x 2
EU/1/20/1443/002 – 5.5 mL vial x 2, 8.3 mL vial x 1
EU/1/20/1443/003 – 5.5 mL vial x 1, 8.3 mL vial x 2
EU/1/20/1443/004 – 8.3 mL vial x 3
EU/1/20/1443/005 – 5.5 mL vial x 2, 8.3 mL vial x 2
EU/1/20/1443/006 – 5.5 mL vial x 1, 8.3 mL vial x 3
EU/1/20/1443/007 – 8.3 mL vial x 4
EU/1/20/1443/008 – 5.5 mL vial x 2, 8.3 mL vial x 3
EU/1/20/1443/009 – 5.5 mL vial x 1, 8.3 mL vial x 4
EU/1/20/1443/010 – 8.3 mL vial x 5
EU/1/20/1443/011 – 5.5 mL vial x 2, 8.3 mL vial x 4
EU/1/20/1443/012 – 5.5 mL vial x 1, 8.3 mL vial x 5
EU/1/20/1443/013 – 8.3 mL vial x 6
EU/1/20/1443/014 – 5.5 mL vial x 2, 8.3 mL vial x 5
EU/1/20/1443/015 – 5.5 mL vial x 1, 8.3 mL vial x 6
EU/1/20/1443/016 – 8.3 mL vial x 7
EU/1/20/1443/017 – 5.5 mL vial x 2, 8.3 mL vial x 6
EU/1/20/1443/018 – 5.5 mL vial x 1, 8.3 mL vial x 7
EU/1/20/1443/019 – 8.3 mL vial x 8
EU/1/20/1443/020 – 5.5 mL vial x 2, 8.3 mL vial x 7
EU/1/20/1443/021 – 5.5 mL vial x 1, 8.3 mL vial x 8
EU/1/20/1443/022 – 8.3 mL vial x 9
EU/1/20/1443/023 – 5.5 mL vial x 2, 8.3 mL vial x 8
EU/1/20/1443/024 – 5.5 mL vial x 1, 8.3 mL vial x 9
EU/1/20/1443/025 – 8.3 mL vial x 10
EU/1/20/1443/026 – 5.5 mL vial x 2, 8.3 mL vial x 9
EU/1/20/1443/027 – 5.5 mL vial x 1, 8.3 mL vial x 10
EU/1/20/1443/028 – 8.3 mL vial x 11
EU/1/20/1443/029 – 5.5 mL vial x 2, 8.3 mL vial x 10
EU/1/20/1443/030 – 5.5 mL vial x 1, 8.3 mL vial x 11
EU/1/20/1443/031 – 8.3 mL vial x 12
EU/1/20/1443/032 – 5.5 mL vial x 2, 8.3 mL vial x 11
EU/1/20/1443/033 – 5.5 mL vial x 1, 8.3 mL vial x 12
EU/1/20/1443/034 – 8.3 mL vial x 13
EU/1/20/1443/035 – 5.5 mL vial x 2, 8.3 mL vial x 12
EU/1/20/1443/036 – 5.5 mL vial x 1, 8.3 mL vial x 13
EU/1/20/1443/037 – 8.3 mL vial x 14

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

OUTER CARTON – VARIABLE DATA (to be printed directly on the outer carton at time of packaging)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zolgensma 2 x 10^{13} vector genomes/mL solution for infusion
onasemnogene abeparvovec
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

EU/1/20/1443/001 – 8.3 mL vial x 2
EU/1/20/1443/002 – 5.5 mL vial x 2, 8.3 mL vial x 1
EU/1/20/1443/003 – 5.5 mL vial x 1, 8.3 mL vial x 2
EU/1/20/1443/004 – 8.3 mL vial x 3
EU/1/20/1443/005 – 5.5 mL vial x 2, 8.3 mL vial x 2
EU/1/20/1443/006 – 5.5 mL vial x 1, 8.3 mL vial x 3
EU/1/20/1443/007 – 8.3 mL vial x 4
EU/1/20/1443/008 – 5.5 mL vial x 2, 8.3 mL vial x 3
EU/1/20/1443/009 – 5.5 mL vial x 1, 8.3 mL vial x 4
EU/1/20/1443/010 – 8.3 mL vial x 5
EU/1/20/1443/011 – 5.5 mL vial x 2, 8.3 mL vial x 4
EU/1/20/1443/012 – 5.5 mL vial x 1, 8.3 mL vial x 5
EU/1/20/1443/013 – 8.3 mL vial x 6
EU/1/20/1443/014 – 5.5 mL vial x 2, 8.3 mL vial x 5
EU/1/20/1443/015 – 5.5 mL vial x 1, 8.3 mL vial x 6
EU/1/20/1443/016 – 8.3 mL vial x 7
EU/1/20/1443/017 – 5.5 mL vial x 2, 8.3 mL vial x 6
EU/1/20/1443/018 – 5.5 mL vial x 1, 8.3 mL vial x 7
EU/1/20/1443/019 – 8.3 mL vial x 8
EU/1/20/1443/020 – 5.5 mL vial x 2, 8.3 mL vial x 7
EU/1/20/1443/021 – 5.5 mL vial x 1, 8.3 mL vial x 8
EU/1/20/1443/022 – 8.3 mL vial x 9
EU/1/20/1443/023 – 5.5 mL vial x 2, 8.3 mL vial x 8
EU/1/20/1443/024 – 5.5 mL vial x 1, 8.3 mL vial x 9
EU/1/20/1443/025 – 8.3 mL vial x 10
EU/1/20/1443/026 – 5.5 mL vial x 2, 8.3 mL vial x 9
EU/1/20/1443/027 – 5.5 mL vial x 1, 8.3 mL vial x 10
EU/1/20/1443/028 – 8.3 mL vial x 11

EU/1/20/1443/029 – 5.5 mL vial x 2, 8.3 mL vial x 10
EU/1/20/1443/030 – 5.5 mL vial x 1, 8.3 mL vial x 11
EU/1/20/1443/031 – 8.3 mL vial x 12
EU/1/20/1443/032 – 5.5 mL vial x 2, 8.3 mL vial x 11
EU/1/20/1443/033 – 5.5 mL vial x 1, 8.3 mL vial x 12
EU/1/20/1443/034 – 8.3 mL vial x 13
EU/1/20/1443/035 – 5.5 mL vial x 2, 8.3 mL vial x 12
EU/1/20/1443/036 – 5.5 mL vial x 1, 8.3 mL vial x 13
EU/1/20/1443/037 – 8.3 mL vial x 14

6. OTHER

Patient Weight
2.6 – 3.0 kg
3.1 – 3.5 kg
3.6 – 4.0 kg
4.1 – 4.5 kg
4.6 – 5.0 kg
5.1 – 5.5 kg
5.6 – 6.0 kg
6.1 – 6.5 kg
6.6 – 7.0 kg
7.1 – 7.5 kg
7.6 – 8.0 kg
8.1 – 8.5 kg
8.6 – 9.0 kg
9.1 – 9.5 kg
9.6 – 10.0 kg
10.1 – 10.5 kg
10.6 – 11.0 kg
11.1 – 11.5 kg
11.6 – 12.0 kg
12.1 – 12.5 kg
12.6 – 13.0 kg
13.1 – 13.5 kg
13.6 – 14.0 kg
14.1 – 14.5 kg
14.6 – 15.0 kg
15.1 – 15.5 kg
15.6 – 16.0 kg
16.1 – 16.5 kg
16.6 – 17.0 kg
17.1 – 17.5 kg
17.6 – 18.0 kg
18.1 – 18.5 kg
18.6 – 19.0 kg
19.1 – 19.5 kg
19.6 – 20.0 kg
20.1 – 20.5 kg
20.6 – 21.0 kg

Date of Receipt:

2D barcode carrying the unique identifier included.
PC:
SN:

NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zolgensma 2 x 10^{13} vector genomes/mL solution for infusion
onasemnogene abeparvovec
Intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5.5 mL
8.3 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Zolgensma 2 x 10^{13} vector genomes/mL solution for infusion
onasemnogene abeparvovec

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child is given this medicine because it contains important information.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor or nurse.
- If your child gets any side effects, talk to your child's doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zolgensma is and what it is used for

What Zolgensma is
Zolgensma is a type of medicine called a 'gene therapy'. It contains the active ingredient onasemnogene abeparvovec which contains human genetic material.

What Zolgensma is used for
Zolgensma is used to treat babies and young children who have a rare, serious inherited condition called 'spinal muscular atrophy' (SMA).

How Zolgensma works
SMA occurs when there is a missing or abnormal version of a gene needed to make an essential protein called 'Survival Motor Neuron' (SMN) protein. Lack of SMN protein causes nerves that control muscles (motor neurons) to die. This results in muscles becoming weak and wasting away, with eventual loss of movement.

Zolgensma works by supplying a fully functioning copy of the SMN gene which then helps the body produce enough SMN protein. The gene is delivered into the cells where it is needed using a modified virus that does not cause disease in humans.

2. What you need to know before your child is given Zolgensma

Do NOT use Zolgensma
Your child **must NOT be given** Zolgensma if they are allergic to onasemnogene abeparvovec or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Your child's doctor will carry out tests for antibodies before treatment to help decide if this medicine is suitable for your child.

Liver problems
Talk to your child's doctor or nurse before your child is given this medicine if your child has had any problems with his/her liver. Zolgensma can cause an immune response that could lead to an increase in enzymes produced by the liver.

Your child will have a blood test to check liver function before starting treatment with Zolgensma. They will also have regular blood tests for at least 3 months after treatment to monitor for increases in liver enzymes.

Respiratory infection
If your child develops a viral respiratory infection (e.g. cold, flu or bronchiolitis) before or after being treated with Zolgensma this could possibly lead to other more serious complications. Signs of a possible viral respiratory infection you need to look out for in your child include coughing, wheezing, sneezing, runny nose, sore throat or fever. Tell your child's doctor straightaway if you notice your child develops any of these symptoms.

Regular blood tests
Zolgensma can lower blood-platelet count (thrombocytopenia). Possible signs of a low blood-platelet count you need to look out for after your child is given Zolgensma include abnormal bruising or bleeding (see section 4 for more information).

Zolgensma may cause raised levels of a heart/cardiac specific protein called 'troponin-I' that may indicate injury to the heart. Possible signs you need to look out for after your child is given Zolgensma include pale grey/blue skin colour, difficulty in breathing, swelling of the limbs or abdomen (see section 4 for more information).

Your child will have a blood test to check blood-platelet count and troponin-I level before starting treatment with Zolgensma. Your child will also have regular blood tests for a period of time after treatment to monitor for changes in blood-platelets and troponin-I levels.

Other medicines and Zolgensma
Tell your child's doctor or nurse if your child is taking, has recently taken or might take any other medicines.

Prednisolone
Your child will also be given a medicine called 'prednisolone' for a period of time (see also section 3) as part of their treatment with Zolgensma. This is a type of medicine called a 'corticosteroid' which will help manage any potential increase in liver enzymes that your child could develop after being given Zolgensma. Your child's doctor will decide if your child should be given prednisolone or another corticosteroid.

Vaccinations
As corticosteroids can affect the body's immune system, **your child's doctor may decide to delay giving some vaccinations** to your child while he/she is receiving prednisolone/corticosteroid treatment. Talk to your child's doctor or nurse if you have any questions.

Zolgensma contains sodium
This medicine contains 4.6 mg sodium per mL, equivalent to 0.23% of the WHO recommended maximum daily intake of 2 g sodium for an adult. Each 5.5 Ml vial contains 25.3 mg sodium, and each 8.3 mL vial contains 38.2 mg sodium.

Additional information for parents/caregiver

Advanced SMA
Zolgensma can rescue viable motor neurons, but does not rescue dead motor neurons. Children with less severe symptoms of SMA (such as absent reflexes or reduced muscle tone) may have sufficient live motor neurons so as to receive significant benefit from Zolgensma treatment. Zolgensma may not work as well in children with severe muscle weakness or paralysis, breathing problems or who are not able to swallow, or in children who have significant malformation (such as heart defects), including patients with SMA Type 0, as these symptoms imply limited potential improvement after treatment with Zolgensma. Your child's doctor will decide if your child should be given this medicine.

Hygiene care
The active substance in Zolgensma may temporarily be excreted through your child's bodily waste. Parents and caregivers should follow good hand-hygiene for up to 1 month after your child is given Zolgensma. Wear protective gloves when coming into direct contact with your child's bodily fluids or waste and wash hands thoroughly afterwards with soap and warm running water, or an alcohol-based hand sanitiser. Double bags should be used to dispose of soiled nappies and other waste. Disposable nappies may still be disposed of in household waste.

You should continue to follow these instructions for at least 1 month after your child's treatment with Zolgensma. Talk to your child's doctor or nurse if you have any questions.

3. How Zolgensma is given

Zolgensma will be given to your child by a doctor or nurse trained in the management of your child's condition.

The amount of Zolgensma your child will receive will be worked out by your child's doctor depending on the child's weight. The dose is measured in units called vector genomes.

The recommended dose is 1.1×10^{14} vector genomes per kg of body weight. This will be given intravenously (into a vein) to your child by a single infusion (drip) over a period of approximately 1 hour.

Zolgensma will be given to your child ONCE only.

Your child will also be given treatment with prednisolone (or another corticosteroid) by mouth, starting 24 hours before being given Zolgensma. The dose of corticosteroid will also depend on your child's weight. The recommended dose of prednisolone is 1 mg per kg body weight daily. Your child's doctor will work out the total dose to give.

Your child will be given corticosteroid treatment daily for approximately 2 months after the dose of Zolgensma, or until your child's increased liver enzymes decrease to an acceptable level. The dose of corticosteroid given to your child will be slowly reduced until treatment can be fully stopped. Your child's doctor will explain when and how they will stop this treatment for your child.

If you have any further questions on the use of Zolgensma or prednisolone ask your child's doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Seek urgent medical attention if your child develops any of the following serious side effects (these occur commonly, i.e. may affect up to 1 in 10 people):

- bruising or bleeding for longer than usual if your child has been hurt - these may be signs of a low blood-platelet count.
- pale grey or blue skin colour, difficulty in breathing (e.g. rapid breathing, shortness of breath), swelling of the limbs or abdomen - these may be signs of possible problems with the heart.

Talk to your child's doctor or nurse if your child develops any other side effects. These can include:

Very common (may affect more than 1 in 10 people)
- increases in liver enzymes (transaminases) seen in blood tests.

Common (may affect up to 1 in 10 people):
- increases in liver enzymes (aspartate aminotransferase, alanine aminotransferase) seen in blood tests;
- vomiting;
- fever.

Reporting of side effects
If your child gets any side effects, talk to your child's doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Zolgensma

Do not use this medicine after the expiry date which is stated on the vial label and carton after EXP. The expiry date refers to the last day of that month.

Vials will be transported frozen (at or below -60ºC).

Upon receipt vials should be refrigerated at 2°C to 8°C immediately, and in the original carton. Zolgensma therapy should be initiated within 14 days of receipt of vials.

6. Contents of the pack and other information

What Zolgensma contains
- The active substance is onasemnogene abeparvovec. Each vial contains onasemnogene abeparvovec with a nominal concentration of 2×10^{13} vg/mL.
- The other ingredients are tromethamine, magnesium chloride, sodium chloride, poloxamer 188, hydrochloric acid (for pH adjustment) and water for injections.

What Zolgensma looks like and contents of the pack
Zolgensma is a clear to slightly opaque, colourless to faint white solution for infusion.

Zolgensma may be supplied in vials containing a nominal fill volume of either of 5.5 mL or 8.3 mL. Each vial is for single use only.

Each carton will contain between 2 to 14 vials.

Marketing Authorisation Holder
AveXis EU Limited
Block B, The Crescent Building
Northwood, Santry
Dublin 9
D09 C6X8
Ireland
Tel: +351 30 88 00 322

Manufacturer
Almac Pharma Services Limited
Finnabair Industrial Estate
Dundalk, Co. Louth
A91 P9KD
Ireland

For any information about this medicine, please contact the Marketing Authorisation Holder.

This leaflet was last revised in

This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine. The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

The following information is intended for healthcare professionals only:

Important: Please refer to the Summary of Product Characteristics (SmPC) before using.

Each vial is for single use only.

This medicinal product contains genetically-modified organisms. Local guidelines on handling of biological waste should be followed.

Handling
- Zolgensma should be handled aseptically under sterile conditions.
- Personal protective equipment (including gloves, safety goggles, laboratory coat and sleeves) should be worn while handling or administering Zolgensma. Personnel should not work with Zolgensma if skin is cut or scratched.
- All spills of Zolgensma must be wiped with absorbent gauze pads and the spill area must be disinfected using a bleach solution followed by alcohol wipes. All clean-up materials must be double bagged and disposed of in accordance with local guidelines on handling of biological waste.
- All materials that may have come in contact with Zolgensma (e.g. vial, all materials used for injection, including sterile drapes and needles) must be disposed of in accordance with local guidelines on handling of biological waste.

Accidental exposure
Accidental exposure to Zolgensma must be avoided.

In case of accidental exposure to skin, the affected area must be thoroughly cleansed with soap and water for at least 15 minutes. In case of accidental exposure to eyes, the affected area must be thoroughly flushed with water for at least 15 minutes.

Storage
Vials will be transported frozen (at or below -60ºC). Upon receipt vials should be refrigerated at 2°C to 8°C immediately, and in the original carton. Zolgensma therapy should be initiated within 14 days of receipt of vials. The date of receipt should be marked on the original carton before the product is stored in the refrigerator.

Preparation
Vials should be thawed before use:

- For packs containing up to 9 vials – thaw for approximately 12 hours in the refrigerator (2ºC to 8ºC) or 4 hours at room temperature (20°C to 25°C).
- For packs containing up to 14 vials – thaw for approximately 16 hours in the refrigerator (2ºC to 8ºC) or 6 hours at room temperature (20°C to 25°C).

Do not use Zolgensma unless thawed.

Once thawed, the medicinal product should not be re-frozen.

After thawing, gently swirl Zolgensma. Do NOT shake.

Do not use this medicine if you notice any particles or discolouration once the frozen product has thawed and prior to administration.

After thawing, Zolgensma should be given as soon as possible.

Administration
Zolgensma should be given to patients ONCE only.

The dose of Zolgensma and exact number of vials required for each patient is calculated according to the patient's weight (see SmPC sections 4.2 and 6.5).

To administer Zolgensma, draw the entire dose volume into the syringe. Once the dose volume is drawn into the syringe it must be administered within 8 hours. Remove any air in the syringe and prepare the infusion bag before administering to the patient via intravenous infusion through a venous catheter. Insertion of a secondary ('back-up') catheter is recommended in case of blockage in the primary catheter.

Zolgensma should be administered with the syringe pump as a single intravenous infusion with a slow infusion of approximately 60 minutes. It should be administered as an intravenous infusion only. It should not be administered as a rapid intravenous injection or bolus. Following completion of infusion, the line should be flushed with saline.

Disposal
Any unused medicinal product or waste material should be disposed of in accordance with local guidelines on handling of biological waste.

Temporary Zolgensma shedding may occur, primarily through bodily waste. Caregivers and patient families should be advised on the following instructions for the proper handling of patient bodily fluids and waste:

- Good hand-hygiene (wearing protective gloves and washing hands thoroughly afterwards with soap and warm running water, or an alcohol-based hand sanitiser) is required when coming into direct contact with patient bodily fluids and waste for a minimum of 1 month after Zolgensma treatment.

- Disposable diapers should be sealed in double plastics bags and can be disposed of in household waste.

Annex IV

Conclusions on the granting of the conditional marketing authorisation presented by the European Medicines Agency

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.