Regulatory Affairs

Zolgensma

Summary of the EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Onasemnogene abeparvovec
Product(s) concerned (brand name(s)):	Zolgensma
Document status:	Final
Version number of the RMP Public Summary:	2.2
Date of final sign off of the RMP Public Summary	02.05.2023

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Zolgensma is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Zolgensma in Switzerland is the “Arzneimittelinformation/ Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Zolgensma.

Table of contents

This is a summary of the risk management plan (RMP) for Zolgensma. The RMP details important risks of Zolgensma, how these risks can be minimized, and how more information will be obtained about Zolgensma's risks and uncertainties (missing information).

Zolgensma's summary of product characteristics (NPI) and its package leaflet give essential information to healthcare professionals and patients on how Zolgensma should be used.

This summary of the RMP for Zolgensma should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Zolgensma's RMP.

I. The medicine and what it is used for

Zolgensma is authorised for the treatment of:

- Patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the survival motor neuron 1 (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 survival motor neuron 2 (SMN2) gene.

It is a gene replacement therapy and it is given by intravenous route. For patients who weigh

2.6 to 21.0 kg, the intravenous dosage is determined by patient body weight with a nominal recommended dose of 1.1×10^{14} vg/kg.

Further information about the evaluation of Zolgensma's benefits can be found in Zolgensma's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/zolgensma.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Zolgensma, together with measures to minimize such risks and the proposed studies for learning more about Zolgensma's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment (if applicable) so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Zolgensma's is not yet available, it is listed under 'missing information' below.

1.1.1 Part VI – II.A: List of important risks and missing information

Important risks of Zolgensma are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Zolgensma. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 13-1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	• Hepatotoxicity • Transient thrombocytopenia • Thrombotic microangiopathy
Important potential risks	• Cardiac adverse events • Use in patients with anti-AAV9 antibody titers > 1:50 and higher vector loads required • Dorsal root ganglia toxicity
Missing information	• Long-term efficacy of onasemnogene abeparvovec therapy • Risks related to off-label use for patients with > 3 SMN2 copies i.e., higher prevalence of anti-AAV9 antibodies and higher vector loads required

II.A: List of important risks and missing information

Important risks of Zolgensma are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Zolgensma. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 13-1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	• Hepatotoxicity • Transient thrombocytopenia • Thrombotic microangiopathy
Important potential risks	• Cardiac adverse events • Use in patients with anti-AAV9 antibody titers > 1:50 and higher vector loads required • Dorsal root ganglia toxicity
Missing information	• Long-term efficacy of onasemnogene abeparvovec therapy • Risks related to off-label use for patients with > 3 SMN2 copies i.e., higher prevalence of anti-AAV9 antibodies and higher vector loads required

II B: Summary of important risks

Table 13-2 Important identified risk: Hepatotoxicity

Evidence for linking the risk to the medicine	**Clinical trials**: Transaminase elevations have been observed without association with clinical signs or symptoms. **Early access programs and post-marketing reports**: Adverse events of transaminase elevations are commonly reported following onasemnogene abeparvovec administration. In the post-marketing setting, cases of ALF have been reported, some of which had fatal outcomes. Patients with impaired liver function
Risk factors and risk groups	**Routine risk minimization measures**: SmPC Sections 4.2, 4.4, 4.8. 5.2, and 5.3
Risk minimization measures	

	Package leaflet (PL) Sections 2, 3, 4 **Additional risk minimization measures**: Healthcare professional guide Caregiver information guide
Additional pharmacovigilance activities	AVXS-101-LT-001, AVXS-101-LT-002, and AVXS-101-RG-001 See Section II.C of this summary for an overview of the post-authorization development plan.

Table 13-3 Important identified risk: Transient thrombocytopenia

Evidence for linking the risk to the medicine	**Clinical trials**: Transient decreases in platelet counts, some of which met the criteria for thrombocytopenia, were observed in onasemnogene abeparvovec clinical studies. In most cases, the lowest platelet value occurred the first week following onasemnogene abeparvovec infusion. **Early access programs and post-marketing reports**: Adverse events of thrombocytopenia or decreased platelet counts are commonly reported after onasemnogene abeparvovec administration. These events are generally not clinically significant. Post-marketing cases with platelet counts < 50 × 10^9/L and <25 x 10^9/L have been reported to occur within two weeks following onasemnogene abeparvovec administration. Unknown
Risk factors and risk groups	**Routine risk minimization measures**: SmPC Sections 4.2, 4.4 and 4.8
Risk minimization measures	PL Sections 2, 4 **Additional risk minimization measures**: Caregiver information guide AVXS-101-LT-001, AVXS-101-LT-002, and AVXS-101-RG-001 See Section II.C of this summary for an overview of the post-authorization development plan.
Additional pharmacovigilance activities	

Table 13-4 Important identified risk: Thrombotic microangiopathy

Evidence for linking the risk to the medicine	Cases of TMA were reported in 23 patients in the post-marketing setting, early access programs, and the registry, cumulatively up to DLP 23-May-2022. Of these, in 12 patients, diagnosis of TMA was supported by available clinical details. All 12 confirmed TMA cases were reported within 1-2 weeks post onasemnogene abeparvovec infusion. TMA is characterized by acute and/or chronic uncontrolled dysregulation and/or excessive activation of the alternative pathway of complement, and its etiology can be genetic or acquired, occurring in both children and adults. TMA is a life-threatening condition, with fatal outcomes reported. In 2020, the incidence of TMA in children is estimated to be three cases/million/year. Although the incidence of TMA in children with SMA is unknown, recent literature suggests coagulation abnormalities can occur inherently in this population. A genetic predisposition to TMA has been associated with mutations in the genes encoding complement factor H, complement factor I, complement factor B, membrane cofactor protein, C3, and

	thrombomodulin, as well as autoantibodies against complement factor H or complement factor I have been reported. In rare conditions, atypical hemolytic uremic syndrome is due to mutation in diacyglycerol kinase ε or deficiency of cobalamin C. Acquired TMA can occur in association with a wide range of viral, bacterial, fungal, and parasitic infections, although it is frequently unclear if this is a direct effect of the pathogen, an adverse reaction to the treatment of an infection, or a trigger that unmasks a latent complement defect. Furthermore, encapsulated organisms have been identified as a trigger; capsular polysaccharide is a critical virulence factor that enables immune evasion. Although an exact mechanism for TMA is unknown, given its rarity in the general population, the number of cases reported for the patients with the rare disease (SMA), and similar pattern of time to onset of TMA, a causal association between onasemnogene abeparvovec and TMA is plausible. Infections and vaccinations
Risk factors and risk groups	**Routine risk minimization measures**: SmPC Sections 4.2, 4.4, 4.8 PL Sections 2, 4
Risk minimization measures	**Additional risk minimization measures**: Healthcare professional guide Caregiver information guide
Additional pharmacovigilance activities	AVXS-101-RG-001, AVXS-101-LT-001, AVXS-101-LT-002 See Section II.C of this summary for an overview of the post-authorization development plan.

Table 13-5 Important potential risk: Cardiac adverse events

Evidence for linking the risk to the medicine	Additional pharmacovigilance activities
Risk factors and risk groups	
Risk minimization measures	

Non clinical: Cardiac degeneration, fibrosis and atrial thrombosis were reported in non-clinical toxicity GLP studies in mice (dosing in mice was higher compared to human dosing). **Clinical**: Cardiac-related non-clinical findings have not been observed in humans.	Minor transient increases in CK-MB and troponin I were reported with no associated clinical sequelae. Cases of tachycardia and bradycardia also occurred. However, the significance of elevated cardiac enzymes or changes in heart rates cannot be determined given the available data. Underlying cardiac abnormalities **Routine risk minimization measures**: SmPC Sections 4.2, 4.4, 4.8, 5.2, 5.3 PL Sections 2, 4 **Additional risk minimization measures**: None AVXS-101-LT-001, AVXS-101-LT-002, and AVXS-101-RG-001 See Section II.C of this summary for an overview of the post-authorization development plan.

Table 13-6 Important potential risk: Use in patients with anti-AAV9 antibody titres > 1:50 and higher vector loads required

Evidence for linking the risk to the medicine	**Clinical**: Patients with AAV9 titres > 1:50 have not been studied in onasemnogene abeparvovec clinical studies. After administration of onasemnogene abeparvovec, increases in anti-AAV9 antibody titres were observed. This is considered an expected response, and there were no apparent relationships between anti-AAV9 antibody titre and safety or efficacy. It is not known whether administration of the onasemnogene abeparvovec vector represents a risk for patients with anti-AAV9 antibodies at higher titres. Patients with anti-AAV9 titres > 1:50 prior to administration of ~~onasemnogene abeparvovec~~.
Risk factors and risk groups	**Routine risk minimization measures**: SmPC Sections 4.2, 4.4, 4.8
Risk minimization measures	**Additional risk minimization measures**: None AVXS-101-RG-001 See Section II.C of this summary for an overview of the post-authorization development plan.
Additional pharmacovigilance activities	

Table 13-7 Important potential risk: Dorsal root ganglia toxicity

Evidence for linking the risk to the medicine	**Clinical**: No adverse events suggestive of ganglionopathy were observed in patients treated with onasemnogene abeparvovec from clinical trials, early access programs, registry and post-marketing clinical experience in whom treatment with steroids was administered. All available autopsy reports of fatal cases in the post marketing setting are being monitored for evidence of DRG toxicity. A limited number of autopsy reports received for the post-marketing cases until 23 May 2022 did not indicate histological evidence of DRG toxicity. **Non-clinical**: In cynomolgus monkeys, i.t. and i.v. administration of onasemnogene abeparvovec has been associated with clinically silent (asymptomatic) microscopic changes in the dorsal root ganglia (DRG) and/or trigeminal ganglia. The findings in the DRG (at all levels) and/or trigeminal ganglia included mononuclear cell inflammation, neuronal degeneration, satellitosis, and/or neuronal necrosis. These non-clinical DRG findings have not been confirmed in patients from both clinical trials as well as post-marketing experience. Based on data accumulated so far from the GLP non-human primate studies at terminal intervals up to 6 weeks post dose, the OAV101-related DRG finding is reclassified from “DRG cell inflammation” to “DRG toxicity” given that the microscopic findings are generally characterized by mononuclear cell inflammation, neuronal degeneration, satellitosis, neuronal loss, gliosis and/or axonal degeneration. In addition, secondary changes in the spinal cord and peripheral nerves of axon degeneration have been observed.
Risk factors and risk groups	Unknown
Risk minimization measures	**Routine risk minimization measures**: SmPC Section 5.3 **Additional risk minimization measures**:

	None
Additional pharmacovigilance activities	AVXS-101-LT-001, AVXS-101-LT-002, and AVXS-101-RG-001 See Section II.C of this summary for an overview of the post-authorization development plan.

Table 13-8 Missing information: Long-term efficacy of onasemnogene abeparvovec therapy

Risk minimization measures	**Routine risk minimization measures**: None **Additional risk minimization measures**: None
Additional pharmacovigilance activities	AVXS-101-LT-001, AVXS-101-LT-002, and AVXS-101-RG-001 See Section II.C of this summary for an overview of the post-authorization development plan.

Table 13-9	Missing information: Risks related to off-label use for patients with > 3 SMN2 copies i.e., higher prevalence of anti-AAV9 antibodies and higher vector loads require
Risk minimization measure	
Additional pharmacovigilance activities	

II C: Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

Table 13-10 Studies which are conditions of the marketing authorization

Study short name	Purpose of the study:
AVXS-101-RG-001: A prospective long-term registry of patients with a diagnosis of SMA (RESTORE)	To assess long-term outcomes in patients with a diagnosis of SMA.

II.C.2. Other studies in post-authorization development plan

Table 13-11 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
AVXS-101-LT-001: Long-term follow-up study for patients from AVXS-101-CL-101 (START)	To collect long-term follow-up safety data of patients with SMA Type 1 who were treated with onasemnogene abeparvovec in the AVXS-101-CL-101 study.
AVXS-101-LT-002: A long term follow up study of patients in the clinical trials for SMA Type 1 Delivering onasemnogene abeparvovec	To collect long term, follow up safety and efficacy data in patients with SMA who were treated with onasemnogene abeparvovec in an onasemnogene abeparvovec clinical trial.