NOVARTIS

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:	1.0
Date of final sign off of the RMP Public Summary	09-Jul-2021

Template version 1.0 Feb 2021

Table of contents

Summary of the risk management plan for Zolgensma (onasemnogene abeparvovec)

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.

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 *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.

Therapy may only be administered up to the age of two years.

It is a gene replacement therapy and it is given by intravenous route. For patients who weigh 2.6 to 16.0 kg, the intravenous dosage is determined by patient body weight with a nominal recommended dose of 1.1×10^{14} vg/kg (See prescribing information for further information).

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 the information for professionals 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.

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 whichthere 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 needsto be collected (e.g. on the long-term use of the medicine).

Table 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 highervector 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 vectorloads required

II B: Summary of important risks

Table 2 Important identified risk: Hepatotoxicity

Evidence for linking therisk 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. Acute serious liver injury or liver failure were reported in 4 cases, which included 2 cases that met the pediatric diagnostic criteria for acute liver failure (ALF; abnormal liver function including coagulopathy, specifically, the INR > 1.5 with clinical evidence of encephalopathy, or INR > 2.0, or INR > 3.0 for neonates without encephalopathy). Additionally, a late-breaking report without a diagnosis of ALF also met the pediatric ALF criteria, adding to 3 cases that met the pediatric ALF criteria. All 3 cases

	meeting the ALF criteria presented with clinical information suggestive of potential pre-existing hepatic abnormalities. Furthermore, 1 of the 3 cases of ALF occurred in the setting of abrupt withdrawal of prednisolone. Recovery from ALF with additional steroid therapy was demonstrated in 2 cases. No follow up data was available for the third case of ALF.
Risk factors and riskgroups	Patients with impaired liver function
Risk minimization measures	**Routine risk minimization measures**: Information for professionals Sections Dosage/Administration, Warnings and precautions, Adverse effects, Pharmacokinetics, Preclinical data Package leaflet (PL) Sections Warnings and precautions, How to use Zolgensma, Possible side effects **Additional risk minimization measures**:Caregiver information guide
Additional pharmacovigilan ceactivities	AVXS-101-LT-001, AVXS-101-LT-002, AVXS 101-CL-304,AVXS-101-CL-302, and AVXS-101-RG-001 See Section II.C of this summary for an overview of thepost-authorization development plan.

Table 3 Important identified risk: Transient thrombocytopenia

Evidence for linking therisk to the medicine	**Clinical trials**: Decreases from baseline in the mean platelet count wereobserved at multiple time points but no clinically significant events (e.g.associated with bleeding) were noted. **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 reports of thrombocytopenia or decreased platelet count have also been received. One post-marketing case of a traumatic bleeding event which lasted overnight before medical attention was reported. The immediate clinical course was complicated with repeated cardiac arrest, disseminated intravascular coagulation and multi-organ failure. Available clinical details demonstrated subsequentimprovement, however the patient died later under unknown clinical circumstances.
Risk factors and riskgroups	Unknown
Risk minimization measures	**Routine risk minimization measures:** Information for professionals Sections Dosage/Administration, Warnings and precautions, Adverse effects PL Sections Sections Warnings and precautions, Possible side effects **Additional risk minimization measures**:None
Additional pharmacovigilan ceactivities	AVXS-101-LT-001, AVXS-101-LT-002, AVXS 101-CL-304,AVXS-101-CL-302, and AVXS-101-RG-001 See Section II.C of this summary for an overview of thepost-authorization development plan.

Table 4 Important identified risk: Thrombotic microangiopathy

Evidence for linking therisk to the medicine	Cases of thrombotic microangiopathy (TMA) were reported for 5 patients as of 23-Nov-2020 in the post-marketing setting, early access programs, and the registry. No TMA cases were reported in clinical trials.

	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. 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, atypicalhemolytic 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, a side effect of treatment,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.
Risk factors and riskgroups	Infections and vaccinations
Risk minimization measures	**Routine risk minimization measures:** Information for professionals Sections Dosage/Administration, Warnings and precautions, Adverse effects PL Sections Warnings and precautions, Possible side effects **Additional risk minimization measures**:Caregiver information guide
Additional pharmacovigilan ceactivities	AVXS-101-RG-001, AVXS-101-LT-001, AVXS-101-LT-002 See Section II.C of this summary for an overview of thepost-authorization development plan.

Table 5 Important potential risk: Cardiac adverse events

Evidence for linking therisk to the medicine	**Non clinical**: Cardiac degeneration, fibrosis and atrial thrombosis werereported in non-clinical toxicity GLP studies in mice (dosing in mice washigher 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 andbradycardia also occurred. However, the significance of elevated cardiac enzymes or changes in heart rates cannot be determined giventhe available data.
Risk factors and riskgroups	Underlying cardiac abnormalities
Risk minimization measures	**Routine risk minimization measures**: Information for professionals Sections Warnings and precautions, Adverse effects, Pharmacokinetics, Preclinical data PL Sections Warnings and precautions, Possible side effects **Additional risk minimization measures**:None
Additional pharmacovigilan ceactivities	AVXS-101-LT-001, AVXS-101-LT-002, AVXS 101-CL-304,AVXS-101-CL-302, and AVXS-101-RG-001 See Section II.C of this summary for an overview of thepost-authorization development plan.

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

Evidence for linking therisk 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.
Risk factors and	Patients with anti-AAV9 titres > 1:50 prior to administration

riskgroups	ofonasemnogene abeparvovec.
Risk minimization measures	**Routine risk minimization measures**: Information for professionals Sections Dosage/Administration, Warnings and precautions, Adverse effects **Additional risk minimization measures**:None
Additional pharmacovigilan ceactivities	AVXS-101-RG-001 See Section II.C of this summary for an overview of thepost-authorization development plan.

Table 7 Important potential risk: Dorsal root ganglia toxicity

Evidence for linking therisk 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. **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 primatestudies 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 riskgroups	Unknown

Risk minimization measures	**Routine risk minimization measures**: Information for professionals Section Preclinical data **Additional risk minimization measures**:None
Additional pharmacovigilan ceactivities	AVXS-101-LT-001, AVXS-101-LT-002, AVXS-101-CL-304,AVXS-101-CL-302, and AVXS-101-RG-001 See Section II.C of this summary for an overview of thepost-authorization development plan.

Table 8 Missing information: Long-term efficacy of onasemnogeneabeparvovec therapy

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

Table 9 Missing information: Risks related to off-label use for patients with > 3 SMN2 copies i.e., higher prevalence of anti-AAV9 antibodiesand higher vector loads required

Risk minimization measures	**Routine risk minimization measures**:None **Additional risk minimization measures**:None
Additional pharmacovigilan ceactivities	None

II C: Post-authorization development plan

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

Table 10 Studies which are conditions of the marketing authorization

Study short name	Purpose of the study:
AVXS-101-CL-304: Pre-symptomatic study of intravenous onasemnogene abeparvovec in SMA for patients with multiple copiesof SMN2 (SPRINT)	To assess efficacy and safety of onasemnogene abeparvovec in patients with SMP type 1, 2, 3 with multiple copies of SMN2 (2, 3, 4)
AVXS-101-CL-302: Gene replacement therapy clinical trial for patients with spinal muscle atrophy type 1(STRIVE-EU)	To characterize the efficacy and safety of onasemnogeneabeparvovec in patients with SMA type 1a and 1b
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 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 fromAVXS-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 trialsfor 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.