الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Saudi Public Assessment Report

(Summary Report)

Zolgensma®

Type of Product: Adeno-associated viral vector-based gene therapy.

Active Pharmaceutical Ingredient(s): Onasemnogene Abeparvovec.

ATC code: M09AX, ther drugs for disorders of the musculo-skeletal system.

Dosage Form: Suspension for injection.

Dosage Strength: $2.0x10^{13}$ vg/mL.

Pack Size: 9.

Shelf life: 12 months.

Storage Conditions: Store in a refrigerator (2°C – 8°C), do not freeze.

Reference Product in SA (if applicable): NA.

Marketing Authorization Holder: Novartis Gene Therapies EU Limited.

Manufacturer: Novartis Gene Therapies, Inc.

Registration No.: 0510222689.

Date of Decision: Approved on 09/05/2022.

Proposed Indications: Treat spinal muscular atrophy, a serious condition of the nerves that causes muscle wasting and weakness.

Product Background

This product is considered as a new viral vector gene therapy, for Saudi regulatory purposes. Furthermore, this product is qualified to follow the SFDA's priority regulatory pathway as it is an orphan medication that was developed for treating spinal muscular atrophy which is a serious condition of the nerves that causes muscle wasting and weakness. The cause of the disease is that the mutated genes do not produce enough Survival Motor Neuron (SMN) protein necessary for normal nerve and muscle function. Zolgensma works by delivering a correct copy of the affected genes known as SMN1, producing an abundance of protein that enables normal nerve function.

The SFDA approval for Zolgensma® (Onasemenogene abeparvovec, 2.0 × 10^{13} vg/mL) is based on a review of the quality, safety and efficacy to meet the last version of SFDA's Data Requirements for Human Drugs Submission as summarised hereinafter:

Quality Aspects

The drug substance contains a transgene that encodes for the human SMN (hSMN) protein. It is comprised of a recombinant adeno-associated virus serotype 9 (AAV9) capsid shell that is engineered to be non-replicating and non-integrating. It contains the DNA of the SMN gene edged by 2 AAV inverted terminal repeats (ITR) from the AAV serotype 2 (AAV2), and cytomegalovirus (CMV) enhancer/chicken-β-actin-hybrid promoter (CB).
The SMN (hSMN) protein is expressed in Human Embryonic Kidney (HEK 293) cells, following a complex process composed mainly from two stages upstream and downstream processing. The whole manufucturing process sufficiently described along with an appropriate process control for critical steps and intermediate. All raw materials involved in the manufucturing process have been listed and categorized into compendial and non-compendial, the non-compendial materials were identified as critical and noncritical based on risk assessment approach. Sufficient data on plasmid manufacturing according to site have been submitted. Drug Substance Release Process Performance Qualification have been submitted to demonstrate process validation using four consecutive runs. As for characterization, elucidation of structure, capsids, and impurities have been studied using a wide range of analytical tools. Drug substance specification parameters are chosen based on characterization studies. The limits have been refined according to pharmaceutical development plan and Process Performance Qualification which performed following *ICH Q8,Q9 and Q10 guidelines*. The analytical procedure has been validated and data were provided.

Zolgensma is a clear to slightly opaque, colourless to faint white solution for infusion. It is a one time treatment administered as an one hour infusion solution. This orphan gene therapy drug is filled in a sterile, ready to use, 10 mL, crystal zenith vial. The vial is sealed with a sterile, chlorobutyl elastomeric stopper. The stopper is capped with a sterile flip-off, aluminum seal with a coloured plastic button cap.

Each mL contains onasemnogene abeparvovec with a nominal concentration of 2×10^{13} vector genomes (vg). Vials 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 customized to meet dosing requirements for individual patients depending on their weight (Zolgensma infusion is administered under sterile conditions). The drug product manufacturing size and batch scale have been demonstrated, stating that the amount of drug product formulation buffer is adjusted accordingly to achieve a target concentration. The dossier contains a detailed justification for the selection of the excipients and their functionality. manufacturing process has been provided, including control of critical steps and intermediates. A 3-stage risk-based approach to the process validation lifecycle has been used as a strategy to validate drug product manufacturing process using four consecutive Process Performance Qualification runs, which have been found suitable to consistently produce material meeting critical quality attributes of the final product. Batch analysis data representing three commercial batches were provided and found to met the latest specification version at the time of submission.

Due to the similarity in formulations between drug substance and drug product, the same reference material is employed for testing both drug substance and drug product.

Nine Drug Product lots manufactured by the commercial manufacturing process have been placed on stability at the long-term storage condition of (≤ -60°C), accelerated storage condition of (2−8°C), and stressed storage condition of (20−25°C). All stability data to date met the proposed stability specification limits at the long-term storage condition of 12 months. Special receiving, handling and administration information that ensure product stability are provided with each shipment.

Clinical Aspects

Efficacy and Safety

The clinical development program for Zolgensma consisted of four pivotal clinical studies: AVXS101-CL-101, AVXS101-CL303, AVXS101-CL304, AVXS101-CL302 efficacy and safety studies.

Summary of the clinical studies presented hereafter:

- AVXS-101-CL-101: phase I, open-label, single-infusion, ascending dose, single-center study. The primary objective is to determine safety based on the development of unacceptable toxicity in 15 subjects with SMA type 1.
- AVXS-101-CL-303: phase III multicenter, open-label, single-arm, single-dose study done to determine the efficacy of AVXS-101 by demonstrating achievement of developmental milestone of functional independent sitting for at least 30 seconds at the 18 months of age study visit and to determine the efficacy of AVXS-101 based on survival at 14 months of age on 22 subjects with SMA type 1 who are < 6 months (< 180 days) of age at the time of gene

replacement therapy (Day 1) with proven biallelic- mutations of the SMN1 gene and 1 or 2 copies of the SMN2.

- AVXS-101-CL-302: phase III open-label, single-arm, single-dose study done to determine efficacy by demonstrating achievement of the developmental milestone of sitting without support for ≥ 10 seconds at any visit up to and including the 18 months of age visit, as defined by WHO Motor Developmental Milestones on 33 subjects with SMA type 1 as determined by diagnosis of SMA based on gene mutation analysis with bi-allelic SMN1 mutations (deletion or point mutations) and 1 or 2 copies of SMN2 [inclusive of the known SMN2 gene modifier mutation (c.859G > C)] and patients must have been < 6 months (< 180 days) of age at the time of AVXS-101 infusion. The primary efficacy endpoint was the achievement of sitting without support for ≥ 10 seconds at any visit up to and including the 18 months of age visit.
- AVXS-101-CL-304: phase III, open-label, single-arm, single-dose study. The primary objective for Cohort 1, who are patients with bi-allelic SMN1 deletions and 2 copies of SMN2 was to assess the efficacy of AVXS-101 by demonstrating functional independent sitting for at least 30 seconds and for Cohort 2, who are patients with bi-allelic SMN1 deletions and 3 copies of SMN2 was to assess the efficacy of AVXS-101 based on the proportion of patients achieving the ability to stand without support for at least 3 seconds. The study included 14 subjects in Cohort 1 and 15 subjects in Cohort 2. Patients population for cohort 1 was patients with 2 copies of SMN2 with pre-symptomatic SMA type 1 and patient populaion for cohort 2 was patients with 3 copies of SMN2 with pre symptomatic SMA type 2.

The clinical pharmacology, efficacy and safety results from the aforementioned studies were assessed by the SFDA efficacy and safety department. Based on the review of the submitted evidence, the benefit/risk balance of Zolgensma is considered positive. Therefore, we recommend the approval of the marketing authorization of Zolgensma.

Product Information

The approved Summary of Product Characteristics (SPC) with the submission can be found in Saudi Drug Information System (SDI) at: https://sdi.sfda.gov.sa/

The date of revision of this text corresponds to that of the Saudi PAR. New information concerning the authorized medicinal product in question will not be incorporated into the Saudi PAR. New findings that could impair the medicinal product's quality, efficacy, or safety are recorded and published at (SDI or Summary Saudi-PAR report).

For inquiry and feedback regarding Saudi PAR, please contact us at Saudi.PAR@sdfa.gov.sa