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Use of Onasemnogene Abeparvovec gene therapy for Spinal Muscular Atrophy

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Abstract

Spinal muscle atrophy (SMA) is an autosomal recessive and neurodegenerative disease caused by homozygous mutations in the survival motor neuron1(SMN 1) gene. SMA isdistinguished by motor neuron degeneration, which is a resulting in weakness and increasing muscle atrophy. Children with a most severe form of SMA there were not able to sit independently.There was only 8% of children would survivebeyond their 2years of age without permanent ventilation support. One of these therapies, Onasemnogene abeparvovec, a gene replacement therapy based on the adeno-related virus, is a one-time intravenous infusion in which it delivers human function SMA. Inadditionto significantly improving survival, Onasemnogene Abeparvovec increases motor function and reducesthe need for respiratory or nutritional support in many patients. Recommendations of Dosage and administration. Recommendations for Prophylaxis of prednisolone tapering and monitoring for potential adverse events, including hepatotoxicity, Elevated Troponin -I thrombotic microangiopathy, are described here.

Table 1.1 Demonstrates a sample for post-treatmentmonitoring. It also describes the Postmarketing experience, drug interactions and their use in a specific population,and even temporary vector shedding and waste handling.

KEYWORDS

Gene therapy, Onasemnogene abeparvovec, efficacy, safety, spinal muscular atrophy

Introduction

Onasemnogene abeparvovec is an adeno-associated virus vector-based (AAV-9) gene therapy it targets motor neuron cells, and it delivers a fully functional copy of the human SMN gene. It improves muscle movement and its function and survival inchildren with SMA throughone-time intravenous administration that results in the expression of SMA protein in child Motor neurons.[1]

On May 24, 2019, the US Food and Drug Administration (FDA) approved Onasemnogene abeparvovec, a medicine for the treatment of spinal muscle wasting (SMA). Zolgensma is a trading name that has been marketed under Novartis which is a Swiss drugmaker and drug developer. This medication has been supported to be utilized in children under 2 years who are confirmed by genetic testing for SMA. [2] The expected treatmentcost is$2.125 million (approximately 14 crore rupees) and the drug is administered as a one-time infusion over 1 hour. This makes it the most expensive drug to be marketed in the world.[3]

In 2019in the United States Onasemnogene abeparvovec was firstly approved for medical usethis medication has been supported to be utilized in children under 2 years old, who are affirmed by hereditary testing for SMA.[4] It was later approved by other authorities with similar scope [5].The approval scope in some other jurisdictions, likeAsia, the European Union, and Canada.[6]

At the time of June 2021, more than 1200 patients have been treated with Onasemnogene abeparvovec worldwide [7]. As more countries and regions approvedIV Onasemnogene abeparvovec, questions have emerged respecting its execution by and by that was not shrouded in the endorsing data or a survey depicting the clinical preliminary experience [8]. This specialist's assessment gives suggestions in key regions by a specialist board of neuromuscular experts who have treated SMA patients with Onasemnogene abeparvovec.[9]

ROLE OF ONASEMNOGENE ABEPARVOVEC

Onasemnogene abeparvovec is an in vivo virus linked to an adenovirus serotype 9 (AAV9) gene replacement therapy that delivers the SMN trans-gene under a ubiquitous promoter into target cells, through a one-time IV infusion.

With one dose, Zolgensma it can stop the progression of SMA.It is designed gene therapy that results to replace the function of missing or non-working SMN 1 gene that causes SMA.

Zolgensma can't cure or reverse the damage that is already caused by SMA before treatment.[4]

In the stage, I START study, treatment of SMA patients less than 8 months of age. Without the requirements ofpermanentventilation which is not seen in natural history, abeparvovec exhibited improvements in survival, which is not seen in natural history, abeparvovec exhibited. improving survival and achieving major milestones.The stage III STR1VE-US study exhibited the advantage-risk profile observed in the stage I study for a larger group. Long-term assessment for up to 5.6 years has demonstratedthe maintaining motor milestones without a new safety signal in patients who have received the targeted therapeutic dose in START.[6]

Children with significant weakness, including those requiring invasive ventilator support, and the potential advantage of treatment in this subgroup of patients may be low because of irreversible loss of motor neurons as the disease progressesOnasemnogene abeparvovec has not been studied [7]. Treatment of patients, involvingthose with the most severe form of SMA who required invasive mechanical ventilation and tracheostomy beforegettingOnasemnogene abeparvovec, has also been reported [8]

WHAT IS SPINAL MUSCULAR ATROPHY (SMA)?

Spinal Muscular Atrophy (SMA) is an autosomal recessive disorder.The genetic cause of SMA is SMN 1 gene that is not working properly or missing that gene [9].That means the body cannot make enough SMN (survivalmotor neuron) protein,which is needed for motor neuron cell survival.Motor neuron cells are responsible for communicating with the legs,throat,arms, and many other areas of the body and let them work together properly.[10] So without enough SMN protein,the motor neuron cells lose their function and may die.As a result, patients with SMA experience difficulty in breathing, speaking, or muscle weakness.[11]

INDICATIONS AND USAGE

ZOLGENSMA is an adeno-associated virus vector-based gene therapy used for pediatrics treatment.[12] the patients below 2 years of old with spinal muscular atrophy (SMA).[13]

Limitations of Use

The repeated administration of Zolgensma for its safety and effectiveness has not been evaluated.[14]

In severe SMA (e.g., complete loss of motionof limbs, long-lasting Ventilation reliance)use of Zolgensma in this understanding has not been accounted for.[15]

DOSAGE AND ADMINISTRATION

Intravenous infusion of single-dose of Zolgensma is used.[16]

Thedose for Zolgensma has been suggested to be**1.1 × 10^{14}** vector genomes per kilogram (vg/kg) of body weight. [17]

Table 1: Dosing

Patient weight Range (kg)	Dose Volume (ml)
26-3.0	16.5
3.1 -3.5	19.3
3.6-4.0	22.0
4.1-5.0	24.8
4.6-5.0	27.5
5.1-5.5	30.3
5.6-6.0	33.0
6.1-6.5	35.8
6.6-7.0	38.5
7.1-7.5	41.3
7.6-8.0	44.0
8.1-8.5	46.8
8.6-9.0	49.5
9.1-9.5	52.3
9.6-10.0	55.0
10.1-10.5	57.8
10.6-11.0	60.5
11.1-11.5	63.3
11.6-12.0	66.0
12.1-12.5	68.8
12.6-13.0	71.5
13.1-13.5(b)	74.3

Dose Volume is calculated:

The patient weight upper limit isa rangefor pediatric patients whoare less than 2 years of age between 2.6 kg and 13.5 kg.[18]

Earlier to ZOLGENSMA infusion:

- Delay ZOLGENSMA in patients with concurrent infections until the infection has resolved due to the increased risk of the serious systemic immune response.[19] Clinicalmanifestations of infection shouldn't be evident at the time of ZOLGENSMA administration.[20]
- Baseline testing should be performed for the presence of anti-AAV9 antibodies.[21]
- Screen liver function of patients.[22]
- Screen creatinine, complete blood count (hemoglobin and platelet count), and troponin-I level.[23]

One day earlier to ZOLGENSMA infusion, oral prednisolone at 1 mg per kg of body weight per day (mg/kg/day) for a total of 30 days [24] infusion which is equivalent to systemic corticosteroids.[25]

Through a venous catheter, a single dose of Zolgensma is administered intravenously.[26]

Follow the steps below for infusion:

- Recommendation of the backup catheter for insertion. A primarycatheter is placed into a vein (generally a peripheral vein in the arm or leg) [28]
- For saline priming program syringe pump, or saline with prime tubing manually.[29]
- Administerslow infusion of Zolgensma over 60 minutes. Don'tinfuse as an intravenouslypushor bolus [30]
- Saline with Flush linefollowing completion of the infusion.[31]

Screening for liver function by clinical examination and by laboratory examinationregularly.

- Check liver status clinically and by assessing ALT, AST, total bilirubin, and prothrombin time after the 30 days of systemic corticosteroids treatment.[32]
- Taper the systemic corticosteroids dose slowly for the next 28 days or longer if needed.Inpatients with unexceptionalfindings (normal clinical exam, total bilirubin, prothrombin time, ALT and AST levels below 2 × upper limit of normal [ULN]): Do not stop systemic corticosteroids all of sudden.[33]
- If liver function abnormalities longer, continuecorticosteroids (equivalent to oral prednisolone at 1 mg/kg/day) until AST and ALT values are both below 2 × ULN and all other evaluation return to normal range, and then taper the corticosteroid dose gradually over the next 28 days or longer if needed.[34] Do not stop systemic corticosteroids all of sudden.[35]
- If liver function abnormalities continue to preserve> 2 × ULN after the 30 days of systemic corticosteroids, consult a pediatric gastroenterologist or hepatologist [36]
- If oraltherapy of corticosteroids is not tolerated, consider intravenous corticosteroids as clinically indicated.[37]

Table 1.1

Sample for post-treatment monitoring schedule

Test	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	We e 12
Liver function	✓	✓	✓	✓		✓		✓		✓		✓
Platelet's count	✓	✓	✓	✓		✓		✓		✓		✓
Troponin -I	✓	✓	✓	✓				✓				✓

✓ = monitoring Performed

Preparation

- Defrost Zolgensma before use. The ingredient of the Zolgensma kit will defrost in around12 hours whenever set in a refrigerator, or around 4 hours if placed at room temperature.[38] If defrost in a refrigerator, take it out from the refrigerator on the day of dosing.
- When defrostZolgensmais a clear to slightly cloudy, colorless to unclearwhite liquid, free of particles [39]. Visually examine vials for particulate matter and discolorationbefore infusion.[40] Do not utilize vials if particulates or discoloration are present.

DO NOT SHAKE.

- Draw the proper dose volume from all vials into a syringe, eliminate air from the syringe, cap the syringe, and take the syringe at room temperature to the patient infusion location. [41]
- Use Zolgensma within 8 hours of drawing into the syringe. Dispose of the vector-containing syringe if the drug is not infused within the 8-hour timeframe. [42]

DO NOT REFREEZE

Laboratory Testing and Monitoring to Estimate Safety.

- Perform baseline anti-AAV9 antibody testing before ZOLGENSMA infusion. If anti-AAV9 antibody titers are reported as > 1:50 then retesting may be done.[43]
- Conduct the following tests at baseline and as givenbelow.[44]
- Liver function (clinical exam, AST, ALT, total bilirubin, prothrombin time) weekly for the first month; on every other week for the 2nd and3rdmonths, until results are average (normal clinical exam, complete bilirubin, and prothrombin results, and ALT and AST levels under 2 × ULN). [45] First-month platelet count doneand then every other week for the 2nd and3rdmonths until platelet counts return to baseline.[46]
- Troponin-I weekly for the 1stmonth, and then monthly for the 2ndand 3rdmonths, until troponin-I levelsreturn to baseline.[47]

DOSAGE FORMS AND STRENGTHS

- ZOLGENSMA is a suspension for intravenous infusion. [48]
- ZOLGENSMA is given in a kit containing 2 to 9 vials. Vials are given in 2 fill volumes: 5.5 mL or 8.3 ml.
- ZOLGENSMA has a minute concentration of 2.0×10^{13}VG/mL, and each vial contains a volume of not less than either 5.5 mL or 8.3 ml. [49]
- The intravenous dosage is determined by patient body weight, with a recommended dose of 1.1×10^{14}mg/kg for pediatric patients.[50]

WARNINGS AND PRECAUTIONS

Acute Serious Liver Injury, Acute Liver Failure or Raised Aminotransferases

- Zolgensma can lead to Acute serious liver injury, acute liver failure, and raisedaminotransferases.The use of Zolgensma inhepatotoxicity (which may be immune-mediated), generally,signifyas raised ALT and/or AST levels and at times as acute liver failure or acute serious liver injuryhas been reported [51]. Toreducepotential aminotransferase elevations, administer systemic corticosteroid to all patients before and after ZOLGENSMA infusion.[52]Immune-mediated hepatotoxicity may necessitate an adjustment to the corticosteroid treatment regimen, including longer.[53]
- Patients with previously liver impairment or acute hepatic viral infection may be at higher risk of acute serious liver injury/acute liver failure.[54] Patients with ALT, AST, or total bilirubin levels (except due to neonatal jaundice) > 2 × ULN have not been studied in clinical trials with

Zolgensma.[55]The risks and benefits of Zolgensma infusion in patients with anterior hepatic insufficiency should be carefully weighed against the risks of not treating the patient. [56]

- Aminotransferase raised were very common in the clinical trials and postmarketing experience, asymptomatic reportedin the managed admittance program and the postmarketing setting, cases of acute serious liver injury, and acute liver failure have been accounted.[57] Some patients have experienced raises in ALT and AST > 20 × ULN, prolonged prothrombin time and have been symptomatic (e.g., vomiting, jaundice), withthe use of prednisolone, can relieve it.Occasionally requires extended duration and/or higher dose.Consult a pediatric gastroenterologist or hepatologist if acute serious liver injury or acute liver failure is suspected.[58]
- **Thrombocytopenia**: Before Zolgensma infusion, monitor platelets count weekly for the 1stmonth and then every other week for the 2ndand3rdmonth until platelet counts return to baseline. [59]
- **Thrombotic Microangiopathy (TMA):** If clinical manifestations and/or laboratory results occur, check with a pediatric hematologist and/or pediatric nephrologist immediately to manage as clinically indicated.[60]
- **Elevated Troponin-I**: Before Zolgensma infusion, Monitor troponin-I weekly for the 1stmonth and then monthly for the 2ndand3rdmonth until troponin-I levelsreturn to baseline.[61]

ADVERSE REACTIONS

Elevated aminotransferases and vomiting are the most common adverse reactions (incidence ≥ 5%) [62].

Postmarketing Experience

During post-approval use of Zolgensma,the following adverse reactions have been identified. Because these reactions are reported spontaneously, it is not always possible to reliably estimate their frequency or determine a causal relationship to drug exposure.[63]

Blood and Lymphatic System Disorders: thrombotic microangiopathy, thrombocytopenia

Hepatobiliary Disorders: acute liver failure, acute liver injury.

General Disorders and Administration Site Conditions: pyrexia

Investigations: troponin increased.[64]

DRUG INTERACTIONS

Where beneficial, adjust a patient's vaccination schedule to accommodate concomitant corticosteroid administration before and following Zolgensma infusion. Some vaccines, such as measles, mumps and rubella (MMR), and chickenpox, are contraindicated in patients receiving the vaccineon a significantly immunosuppressive steroid dose (i.e., ≥ 2 weeks of daily intake of 20 mg or 2 mg/kg body weight of prednisone or equivalent). Prophylaxis is not precluded for Seasonal RSV.[65]

USE OF ZOLGENSMA IN SPECIFIC POPULATIONS

1. **Pregnancy**

There are no reported data regarding Zolgensma use in pregnant women. [66]

2. **Lactation**

There is no information report on the presence ofhuman milk, the effects on the breast-fed infant, or the effects on milk production. The formative and health benefits of breastfeeding must be considered, as well as the clinical need for Zolgensma from the mother and any possible adverse effects.[67]

3. **Pediatric Use**

Administration of Zolgensma to premature neonatesis not recommended, before reaching full-termbecause concurrent treatment with corticosteroids can be detrimental to neurological development. Postpone Zolgensma infusion until the corresponding full-term gestational age is reached.[68]

Patients who received ZOLGENSMA infusion at age 0.3 to 7.9 months (weight range 3.0 kg to 8.4 kg).The safety of Zolgensma was studied in pediatrics.

Patients who received ZOLGENSMA infusion at age 0.5 to 7.9 months (weight range 3.6 kg to 8.4 kg).The efficacy of ZOLGENSMA was studied in pediatrics.

4. **Hepatic Impairment**

Patients with liver impairmentZolgensma therapy should be considered carefully. Patients with preexisting liver abnormalities cases of acute serious liver injury and acute liver failure have been reported with Zolgensma. In clinical trials, raised of aminotransferases was observed in patients following ZOLGENSMA infusion.[69]

TEMPORARY VECTOR SHEDDINGAND WASTE HANDLING

Impermanent vector shedding of Zolgensma happens basically throughbody waste. Informcaregivers on the proper handling of patient feces; suggest procedures include sealing disposable diapers in disposable trash bags and then disposing into the regular trash. Give guidelines to caregivers and family members regarding proper hand hygiene when coming into direct contact with patient body waste. These precautions should be followed for not less than 1 month after Zolgensma infusion.[70]

CONCLUSIONS

Onasemnogene abeparvovec provides a quick and supportive improvement in motor function for young children less than 2 years of agewith type 1 SMA and extends their lives.Zolgensma provides a novel, successful treatment that has assisted infants to achieved for example inhaling without a ventilator, sitting up on all alone crawling, and walking after a single doseinfusion treatment. This deal is a life-changer for young people with this severe illness and their families. More patients seek this inventive therapy, treatment centers should prepare to deal with and manage the drug. Given the dynamicidea of SMA and the need to start treatment before irreversible motor neuron loss, doctors should be able to distinguish those patients eligible to receive. Concerns include world costlier medicine and potential liver toxicity. Long-term advantages and risks have not been determined.

DECLARATIONS

Ethics approval and consent to participate

Not Applicable

Consent for publication

Not Applicable

Availability of data and material

The review work has been carried out by us and we assure you that it can be provided to you whenever required.

Conflict of Interest

Declared None.

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Competing interests

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Authors' contributions

We have assured that "all authors have read and approved the manuscript". All the authors have equal contribution and participation in this research work.

REFERENCE

1. Mahajan, R. (2019). Onasemnogene abeparvovec for spinal muscular atrophy: The costlier drug ever. International Journal of Applied & Basic Medical Research, 9(3), 127–128. https://doi.org/10.4103/ijabmr.IJABMR_190_19.
2. Saha, D. D., Nandi, K., Chakraborty, A., & Jyoti Sen, D. D. (2021). Zolgensma: World's most expensive drug of choice; Survival of Motor Function for the Treatment of Spinal Muscular Atrophy Type 1. World Journal of Pharmaceutical Sciences, 09(11), 83–86.
3. US Food and Drug Administration. FDA News Release – FDA Approves Innovative Gene Therapy to Treat Pediatric Patients with Spinal Muscular Atrophy, a Rare Disease and Leading Genetic Cause of Infant Mortality. US Food and Drug Administration. 2019. May 24, [Last accessed on 2019 Jun 03]
4. The Hindu. FDA Okays $2M Medicine, Most Expensive Ever. [Last accessed on 2019 Jun 03].
5. Ehrhardt A, Xu H, Kay MA. Episomal persistence of recombinant adenoviral vector genomes during the cell cycle in vivo. J Virol. 2003;77: 7689-7695.
6. Nault JC, Datta S, Imbeaud S, et al. Recurrent AAV2-related insertional mutagenesis in human hepatocellular carcinomas. Nat Genet. 2015; 47:1187-1193.
7. Nakia H, Montini E, Fuess S, et al. Helper-independent and AAV-ITR-independent chromosomal integration of double-stranded linear DNA vectors in mice. Mol Ther. 2003; 7:101-111.
8. Al-Zaidy SA, Mendell JR. From clinical trials to clinical practice: practi-cal considerations for gene replacement therapy in SMA type 1. Pediatr Neurol. 2019; 100:3-11.
9. ZOLGENSMA® (onasemnogene abeparvovec-xioi). (n.d.). ZOLGENSMA. Retrieved January 3, 2022.
10. Mendell JR, Al-Zaidy SA, Lehman KJ, et al. Five-year extension results of the phase I START trial of onasemnogene abeparvovec in spinal muscular atrophy. JAMA Neurol. 2021; 78:834-841.

11. Harada Y, Rao VK, Arya K, et al. Combination molecular therapies for type 1 spinal muscular atrophy. Muscle Nerve. 2020; 62:550-554.
12. Matesanz SE, Curry C, Gross B, et al. Clinical course in a patient with spinal muscular atrophy type 0 treated with nusinersen and onasemnogene abeparvovec. J Child Neurol. 2020; 35:717-723.
13. Day JW, Finkel RS, Chiriboga CA, et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy with two copies of SMN2 (STR1VE): an open-label, single-arm, phase 3 study. Lancet Neurol. 2021; 20:284-293.
14. Abreu NJ, Waldrop MA. Overview of gene therapy in spinal muscular atrophy and Duchenne muscular dystrophy. Pediatr Pulmonol. 2021 Apr;56(4):710-720. Doi: 10.1002/ppul.25055. Epub 2020 Sep 14. PMID: 32886442.
15. Harada Y, Rao VK, Arya K, et al. Combination molecular therapies for type 1 spinal muscular atrophy. Muscle Nerve. 2020; 62:550-554.
16. Matesanz SE, Curry C, Gross B, et al. Clinical course in a patient with spinal muscular atrophy type 0 treated with nusinersen and onasemnogene abeparvovec. J Child Neurol. 2020; 35:717-723.
17. American College of Clinical Pharmacy. Reference values for common laboratory tests. Pediatric Self-Assessment Program (PSAP). Accessed October 12, 2020.
18. Chand D, Mohr F, McMillan H, et al. Hepatotoxicity following admin-istration of onasemnogene abeparvovec (AVXS-101) for the treat-ment of spinal muscular atrophy. J Hepatol. 2021; 74:560-566.
19. Babuin L, Jaffe AS. Troponin: the biomarker of choice for the detec-tion of cardiac injury. CMA. 2005; 173:1191-1202.
20. CA, Blank AC, Stam M, Wadman RI, van den Berg LH, van der Pol WL. Cardiac pathology in spinal muscular atrophy: a systematic review. Orphanet J Rare Dis. 2017; 12:67.
21. S, Cuisset JM, Marret S, et al. Type 0 spinal muscular atrophy: further delineation of prenatal and postnatal features in 16 patients. J Neuromuscul Dis. 2016; 3:487-495.
22. Medicines Agency. Committee for Medicinal Products for Human Use and Committee for Advanced Therapies. Assessment report: Zolgensma. Updated March 26, 2020.
23. Bohn MK, Higgins V, Kavsak P, et al. High-sensitivity generation 5 car-diac troponin T sex-and age-specific 99th percentiles in the CALIPER cohort of healthy children and adolescents. Clin Chem. 2019;65: 589-591.
24. Bader D, Kugelman A, Lanir A, et al. Cardiac troponin I serum concen-trations in newborns: a study and review of the literature. Clin Chim Acta. 2006; 371:61-65.
25. Chirmule N, Propert K, Magasin S, Qian Y, Qian R, Wilson J. ImmuneResponses to adenovirus and adeno-associated virus inhumans. GeneTher.1999;6:1574-1583.
26. Waldrop MA, Karingada C, Storey MA, Powers B, Iammarino MA, Miller NF, Alfano LN, Noritz G, Rossman I, Ginsberg M, Mosher KA, Broomall E, Goldstein J, Bass N, Lowes LP, Tsao CY,

Mendell JR, Connolly AM. Gene Therapy for Spinal Muscular Atrophy: Safety and Early Outcomes. Pediatrics. 2020 Sep;146(3): e20200729. Doi: 10.1542/peds.2020-0729. PMID: 32843442.

27. Kichula, E. A., Proud, C. M., Farrar, M. A., Kwon, J. M., Saito, K., Desguerre, I., & McMillan, H. J. (2021). Expert recommendations and clinical considerations in the use of onasemnogene abeparvovec gene therapy for spinal muscular atrophy. Muscle & Nerve, 64(4), 413–427. https://doi.org/10.1002/mus.27363
28. Burghes AH, Beattie CE. Spinal muscular atrophy: why do low survival motor neuron protein levels make motor neurons sick? Nat Rev Neurosci. 2009; 10:597-609.
29. Zolgensma (onasemnogene abeparvovec-xioi). Package insert. AveXis, Inc, 2021. zolgensma.pdf. Accessed March 19, 2021
30. (N.d.). Fda.Gov. Retrieved January 3, 2022.
31. DailyMed – ZOLGENSMA- onasemnogene abeparvovec-xioi kit. (n.d.). Nih.Gov. Retrieved January 3, 2022.
32. American College of Clinical Pharmacy. Reference values for common laboratory tests. Pediatric Self-Assessment Program (PSAP). Accessed October 12, 2020.
33. AusPAR -ZOLGENSMA -onasemnogene abeparvovec -Novartis Pharmaceuticals Australia Pty Ltd -PM-2019-05979-1-3 FINAL. (2021). Gov.Au.
34. DailyMed. (2015). Choice (Chicago, Ill.), 52(10), 52-5368-52–5368.
35. Gahart, B. L., Nazareno, A. R., & Ortega, M. (2019). Gahart's 2020 intravenous medications – E-book: A handbook for nurses and health professionals (36th ed.). Elsevier.
36. (N.d.-d). Pharmaline.Co.Il. Retrieved January 3, 2022.
37. ZOLGENSMA® (onasemnogene abeparvovec-xiii) suspension, for intravenous infusion Initial U.S. Approval: 2019. (n.d.). Nih.Gov. Retrieved January 4, 2022.
38. Zolgensma – side effects, uses, dosage, overdose, pregnancy, alcohol. (2019, July 25). Medicineshoppe.Com.
39. Brighton Center for Pediatric Neurodevelopment. Retrieved January 4, 2022.
40. Department of Health and Human Services, National Institutes of Health. NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines). Bethesda, MD: NIH Office of Science Policy; April 2019.
41. Chand DH, Finkel RS, Mercuri E, et al. Intravenous onasemnogene abeparvovec for spinal muscular atrophy: cumulative safety report. The Cure SMA Annual Conference is a virtual presentation, June 8-12, 2020.
42. Prabhu N, Salam E, Louis C, et al. Thrombotic microangiopathy (TMA): a potential adverse reaction post-Zolgensma (onasemnogene abeparvovec-xiii) therapy for spinal muscular atrophy (SMA) (5483). Neurology. 2020;94(suppl 15):5483.

43. US Centers for Disease Control and Prevention. National Institutes of Health. Biosafety in Microbiological and Biomedical Laboratories. 6th ed. Atlanta, GA: CDC; June 2020.
44. Waldrop MA, Elsheikh BH. Spinal muscular atrophy in the treatment era. Neurol Clin. 2020; 38:505-518.
45. Asher DR, Thapa K, Dharia SD, et al. Clinical development on the frontier: gene therapy for Duchenne muscular dystrophy. Expert Opin Biol Ther. 2020; 20:263-274.
46. RS, Mercuri E, Meyer OH, et al. Diagnosis and management of spinal muscular atrophy: Part 2: pulmonary and acute care; medica-tions, supplements, and immunizations; other organ systems; and ethics. Neuromuscul Disord. 2018; 28:197-207.
47. Medical Device Evaluation Division. Pharmaceutical Safety and Envi-ronmental Health Bureau. Ministry of Health, Labour and Welfare. Report on the deliberation results.
48. European Medicines Agency. Annex I: Summary of product characteris-tics. zolgensma-par-product-information_en.pdf. Accessed November 2, 2020.
49. Australian Product Information—Zolgensma® (onasemnogene abe-parvovec) for single-dose intravenous infusion only. https://www.Novartis.com.au/system/files/product-info/zol240221i.pdf. Accessed March 18, 2021.
50. Product Monograph Including Patient Medical Information—Zolgensma™ (onasemnogene abeparvovec) solution for intravenous infusion, 2 □ 1013 vector genomes/ml. 1747. Accessed June 9, 2021.
51. Gernoux G, Gruntman AM, Blackwood M, Zieger M, Flotte TR, Mueller C. Muscle-Directed Delivery of an AAV1 Vector Leads to Capsid-Specific T Cell Exhaustion in Nonhuman Primates and Humans. Mol Ther. 2020 Mar 4;28(3):747-757. Doi: 10.1016/j.ymthe.2020.01.004. Epub 2020 Jan 13. PMID: 31982038; PMCID: PMC7054721.
52. Emmanuel SN, Smith JK, His J, Tseng YS, Kaplan M, Mietzsch M, Chipman P, Asokan A, McKenna R, Agbandje-McKenna M. Structurally Mapping Antigenic Epitopes of Adeno-Associated Virus 9: Development of Antibody Escape Variants. J Virol. 2021 Nov 10: JVI0125121. Doi: 10.1128/JVI.01251-21. Epub ahead of print. PMID: 34757842.
53. Vu-Han TL, Weiß C, Pumberger M. Novel therapies for spinal muscular atrophy is likely changing the patient phenotype. Spine J. 2020 Dec;20(12):1893-1898. Doi: 10.1016/j.spinee.2020.08.013. Epub 2020 Aug 25. PMID: 32858169.
54. Gorovits B, Azadeh M, Buchli's G, Harrison T, Havert M, Jawa V, Long B, McNally J, Milton M, Nelson R, O'Dell M, Richards K, Vettermann C, Wu B. Evaluation of the Humoral Response to Adeno-Associated Virus-Based Gene Therapy Modalities Using Total Antibody Assays. AAPS J. 2021 Sep 16;23(6):108. Doi: 10.1208/s12248-021-00628-3. PMID: 34529177; PMCID: PMC8445016.

55. Servais L, Baranello G, Scoto M, Daron A, Oskoui M. Therapeutic interventions for spinal muscular atrophy: preclinical and early clinical development opportunities. Expert Opin Investig Drugs. 2021 May;30(5):519-527. Doi: 10.1080/13543784.2021.1904889. Epub 2021 Apr 13. PMID: 33749510.
56. Pierzchlewicz K, Kępa I, Podogrodzki J, Kotulska K. Spinal Muscular Atrophy: The Use of Functional Motor Scales in the Era of Disease-Modifying Treatment. Child Neurol Open. 2021 Apr 27; 8:2329048X211008725. Doi: 10.1177/2329048X211008725. PMID: 33997096; PMCID: PMC8107939.
57. Jensen TL, Gøtzsche CR, Woldbye DPD. Current and Future Prospects for Gene Therapy for Rare Genetic Diseases Affecting the Brain and Spinal Cord. Front Mol Neurosci. 2021 Oct 6; 14:695937. Doi: 10.3389/fnmol.2021.695937. PMID: 34690692; PMCID: PMC8527017.
58. Ravi B, Chan-Cortés MH, Sumner CJ. Gene-Targeting Therapeutics for Neurological Disease: Lessons Learned from Spinal Muscular Atrophy. Annu Rev Med. 2021 Jan 27; 72:1-14. Doi: 10.1146/annual-med-070119-115459. PMID: 33502897.
59. Keinath MC, Prior DE, Prior TW. Spinal Muscular Atrophy: Mutations, Testing, and Clinical Relevance. Appl Clin Genet. 2021 Jan 25; 14:11-25. Doi: 10.2147/TACG.S239603. PMID: 33531827; PMCID: PMC7846873.
60. Naveed A, Calderon H. Onasemnogene Abeparvovec (AVXS-101) for the Treatment of Spinal Muscular Atrophy. J Pediatr Pharmacol Ther. 2021;26(5):437-444. Doi: 10.5863/1551-6776-26.5.437. Epub 2021 Jun 28. PMID: 34239394; PMCID: PMC8244960.
61. Kotulska K, Fattal-Valevski A, Haberlova J. Recombinant Adeno-Associated Virus Serotype 9 Gene Therapy in Spinal Muscular Atrophy. Front Neurol. 2021 Oct 13; 12:726468. Doi: 10.3389/fneur.2021.726468. PMID: 34721262; PMCID: PMC8548432.
62. Kolb SJ, Coffey CS, Yankey JW, et al. Natural history of infantile-onset spinal muscular atrophy. Ann Neurol 2017;82(6):883e91.
63. Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. N Engl J Med 2017;377(18): 1723e32.
64. Dyer O. Health ministers condemn Novartis lottery for Zolgensma, the world's most expensive drug. BMJ. 2020 Feb 12;368:m580. Doi: 10.1136/BMJ.m580. PMID: 32051111.
65. Keeler AM, Flotte TR. Recombinant Adeno-Associated Virus Gene Therapy in Light of Luxturna (and Zolgensma and Glybera): Where Are We, and How Did We Get Here? Annu Rev Virol. 2019 Sep 29;6(1):601-621. Doi: 10.1146/annual-virology-092818-015530. Epub 2019 Jul 5. PMID: 31283441; PMCID: PMC7123914.
66. Stevens D, Claborn MK, Gildon BL, Kessler TL, Walker C. Onasemnogene Abeparvovec-xiii: Gene Therapy for Spinal Muscular Atrophy. Ann Pharmacother. 2020 Oct;54(10):1001-1009. Doi: 10.1177/1060028020914274. Epub 2020 Mar 23. PMID: 32204605.

67. Kirschner J, Butoianu N, Goemans N, Haberlova J, Kostera-Pruszczyk A, Mercuri E, van der Pol WL, Quijano-Roy S, Sejersen T, Tizzano EF, Ziegler A, Servais L, Muntoni F. European ad-hoc consensus statement on gene replacement therapy for spinal muscular atrophy. Eur J Paediatr Neurol. 2020 Sep; 28:38-43. Doi: 10.1016/j.ejpn.2020.07.001. Epub 2020 Jul 9. PMID: 32763124; PMCID: PMC7347351.
68. Nidetz NF, McGee MC, Tse LV, Li C, Cong L, Li Y, Huang W. Adeno-associated viral vector-mediated immune responses: Understanding barriers to gene delivery. Pharmacol Ther. 2020 Mar; 207:107453. Doi: 10.1016/j.pharmthera.2019.107453. Epub 2019 Dec 11. PMID: 31836454; PMCID: PMC6980784.
69. Barkats M. Amyotrophie spinale infantile – De la découverte du gène à la thérapie génique [SMA: from gene discovery to gene therapy]. Med Sci (Paris). 2020 Feb;36(2):137-140. French. Doi: 10.1051/medsci/2020010. Epub 2020 Mar 4. PMID: 32129749.
70. Nance JR. Spinal Muscular Atrophy. Continuum (Minneap Minn). 2020 Oct;26(5):1348-1368. Doi: 10.1212/CON.0000000000000918. PMID: 33003005.

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