CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213026Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	213026
PDUFA Goal Date	02/25/2021
OSE RCM #	2020-1342
Reviewer Name(s)	Ingrid N. Chapman, Pharm.D., BCPS
Team Leader	Jacqueline Sheppard, Pharm.D.
Deputy Division Director	Doris Auth, Pharm.D.
Review Completion Date	02/16/2021
Subject	Evaluation of Need for a REMS
Established Name	Casimersen
Trade Name	Amondys 45
Name of Applicant	Sarepta Therapeutics, Inc.
Therapeutic Class	Antisense oligonucleotide
Formulation(s)	100 mg/2 mL single dose vial (solution for injection)
Dosing Regimen	30 mg/kg IV once weekly

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity, Amondys 45 (casimersen) is necessary to ensure the benefits outweigh its risks. Sarepta Therapeutics, Inc. submitted a New Drug Application (NDA 213026) for casimersen with the proposed indication: for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation in the DMD gene that is amenable to exon 45 skipping. The risk associated with casimersen include kidney toxicity. The Applicant did not submit a proposed REMS or risk management plan with this application.

The Division of Risk Management (DRM) and the Division of Neurology 1 (DN1) agree that a REMS is not needed to ensure the benefits of casimersen outweigh its risks. Casimersen meets the accelerated approval criteria by having the potential to address an unmet medical need in a serious condition based on the surrogate endpoint, dystrophin protein. Other antisense oligonucleotides (ASOs) approved via accelerated approval for the treatment of DMD include eteplirsen, golodirsen, and viltolarsen. Casimersen has similar risks to these ASOs including the risk of kidney toxicity. Prescribers are likely to be familiar and able to appropriately monitor for this risk. Additionally, kidney toxicity will be included in the Warnings and Precautions section of the casimersen label with monitoring recommendations.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME), Amondys 45 (casimersen) is necessary to ensure the benefits outweigh its risks.[a] Sarepta Therapeutics, Inc submitted a New Drug Application (NDA 213026) for casimersen with the proposed indication: for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation in the DMD gene that is amenable to exon 45 skipping. This application is under review in the Division of Neurology 1 (DN1). The Applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Amondys 45 (casimersen), a new molecular entity, is an antisense oligonucleotide proposed for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation in the DMD gene that is amenable to exon 45 skipping.[1] Casimersen is proposed as a 100 mg/2 mL sterile solution for injection in a single dose vial. The recommended dose is 30 mg/kg once weekly administered by intravenous infusion over 35 to 60 minutes. Treatment is continued indefinitely.[b] Casimersen is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 213026 relevant to this review:

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- 07/21/2014: Fast Track Designation granted for casimersen under IND 118086.
- 06/25/2020: NDA 213026 submission for casimersen for the treatment of Duchenne muscular dystrophy received.
- 10/19/2020: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for casimersen.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

DMD is an inherited, X-linked recessive condition caused by mutations of the dystrophin gene. The majority of mutations are deletions that cause a disruption in the mRNA reading frame and prevent the production of functional dystrophin. The absence of dystrophin causes degeneration of muscle fibers, inflammation, and replacement of muscle by fibrotic and adipose tissue. DMD affects males more than females and is estimated to occur in approximately 16 live male births per 100,000 in the U.S.[2,c] Symptoms usually present in early childhood and may include delayed motor development, enlarged calf muscles, progressive muscle weakness, toe walking or waddling gait, and cardiomyopathy. Patients often lose ambulation before 12 years of age and require noninvasive ventilation by late teenage years.[3] Despite advances in therapy, survival beyond the third decade is uncommon.[d]

3.2 Description of Current Treatment Options

Non-pharmacologic treatment for DMD includes physical therapy to encourage mobility, regular submaximal aerobic exercise for those who are ambulatory or in the early non-ambulatory phase, and nutrition management.[3] Additionally, orthopedic interventions are recommended to maintain function and prevent contractures.

The mainstay of pharmacologic treatment for DMD is traditionally glucocorticoids (e.g. prednisone and deflazacort).[4] Deflazacort is FDA-approved (2017) for the treatment of DMD in patients 2 years of age and older.[5] Glucocorticoids are recommended in children to improve motor function, strength, pulmonary function, reducing scoliosis, and delaying loss of ambulation. Novel, genetic therapies that increase dystrophin expression by exon skipping include the antisense oligonucleotides eteplirsen, golodirsen, and viltolarsen.[4] These agents use increased dystrophin expression in skeletal muscle as a surrogate marker for clinical benefit. Because these three ASOs were approved under accelerated approval regulations, further adequate and well-controlled clinical trials to verify and describe clinical benefit are required.[6]

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*
[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

Table 1:[4] FDA-Approved Therapies for the Treatment of DMD

Drug (Approval Date)	Indication	Dosing and Administration	Important Safety & Tolerability Issues	Risk Management Approaches
Exondys 51 - eteplirsen (09/19/2016)	Treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping	30 mg/kg IV once weekly	Hypersensitivity reactions	Labeling – Warnings & Precautions
Emflaza – Deflazacort (02/09/2017)	Treatment of DMD in patients ≥ 2 years of age	0.9 mg/kg once daily	Adrenal suppression Immunosuppression Thyroid disease Cardiovascular disease Gastrointestinal disease Psychiatric disturbances Osteoporosis Kaposi Sarcoma Thromboembolic events	Labeling – Warnings & Precautions
Vyondys 53 – golodirsen (12/12/2019)	Treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping	30 mg/kg IV once weekly	Hypersensitivity reactions Renal toxicity	Labeling – Warnings & Precautions
Viltepso – viltolarsen (09/02/2020)	Treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping	80 mg/kg by IV infusion once weekly	Renal toxicity	Labeling – Warnings & Precautions

4 Benefit Assessment

The efficacy of casimersen for the treatment of DMD was demonstrated in one Phase 3 study (4045-301) and one long-term extension (LTE) study (4045-302).[7] Both studies enrolled patients with genotypically confirmed DMD with deletion mutations amenable to skipping exon 45 or 53. Active drug was either casimersen or golodirsen based on the deletion mutation type. The dosing regimen for casimersen and golodirsen was the same in both studies, 30 mg/kg administered intravenously once weekly. Patients had to be on a stable dose of oral corticosteroids for at least 24 weeks prior to receiving casimersen. Both studies were ongoing at the end of May 2019, which was the stopping point for collecting data submitted in this NDA (i.e., the data cut-off). For the purpose of this review, only casimersen is discussed.

Study 4045-301 is a Phase 3, double-blind, placebo-controlled, multicenter study with an open-label

extension to evaluate the efficacy and safety of casimersen or golodirsen. In part 1 (double-blind; placebo-controlled) of Study 4045-301, patients were randomized in a 2:1 ratio, active casimersen or golodirsen to matching placebo, with a treatment duration of 96 weeks. Thereafter, all patients begin part 2 (open-label treatment extension) consisting of active treatment according to their genotype for up to 48 weeks.

Two endpoint types were utilized for this study, efficacy endpoints and biological endpoints. The primary efficacy endpoint was Change from Baseline (CFB) to Week 96 in the 6 Meter Walk Test (6MWT).[e] However, because the study was ongoing at the time of the NDA submission, this data was not submitted. The FDA agreed the Applicant could submit data for dystrophin protein, as a surrogate biological endpoint.[8] The primary biological endpoint was CFB to Week 48 in dystrophin protein levels expressed in muscle biopsy samples as determined by Western blot. Another biological endpoint was CFB at Week 48 in exon skipping by measurement and sequence verification of exon 45 skipped mRNA.

For the primary biological endpoint of dystrophin protein (casimersen: N = 27; placebo: N = 16), results from the interim analysis showed a mean change of 0.811% for casimersen and 0.217% for placebo; mean difference of 0.594% ($p = 0.004$), which was statistically significant.[9] The casimersen group also had a greater increase in percent exon 45 skipping from Baseline to Week 48 than the placebo group (mean change of 1.606% for casimersen and 0.007% for placebo; $p < 0.001$).[9] Whether increased dystrophin protein translates into a clinically meaningful benefit is unknown until the Applicant's ongoing clinical studies have been completed, and clinically meaningful endpoints can be evaluated.[8]

Study 4045-302 is an LTE study in patients who have completed participation in a clinical trial evaluating casimersen or golodirsen. Treatment is administered for up to 144 weeks. Study results were not submitted with this NDA.

The Clinical reviewer commented that the results from Study 4045-301 meet the statutory evidentiary standards to grant accelerated approval of casimersen for the treatment of DMD amenable to exon 45 skipping. The Clinical Reviewer recommends approval due to the potential benefit of increased dystrophin production in casimersen-treated patients.[8]

5 Risk Assessment & Safe-Use Conditions

The safety profile of casimersen was derived from the two ongoing efficacy studies and Study 4045-101. Study 4045-101 was a small, Phase 1, double-blind, placebo-controlled, multi-centered study in patients with DMD amenable to exon 45 skipping.[10] The study determined the pharmacokinetics of casimersen and evaluated the safety and tolerability of four escalating doses (4 mg/kg, 10 mg/kg, 20 mg/kg, and 30 mg/kg) administered once weekly. Study 4045-101 included a double-blind period (12 weeks) and an open-label period (132 weeks). In the double-blind, placebo-controlled period, 12 patients were randomized (casimersen = 12; placebo = 4). All 12 patients received casimersen 30 mg/kg IV once weekly in the open-label period.

[e] Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

At the time of the data cut-off, the safety database included 76 casimersen-treated patients and 35 placebo-treated patients. The most common adverse reactions for patients treated with casimersen were pyrexia, cough, headache, upper respiratory tract infection, arthralgia, and oropharyngeal pain.[11] The incidence of any serious adverse events (SAES) occurred in 22.4% of casimersen-treated patients and 17.1% in the placebo-treated patients.[f] See Table 2 for specific SAES.

Table 2:[8] Serious Adverse Events by Preferred Term

Preferred Term	Placebo (N = 35)	Casimersen (N = 76)
Number of Patients with at least one Treatment-Emergent Serious Adverse Event	6 (17.1%)	17 (22.4%)
Cardiac Arrest	0	1 (1.3%)
Hydrocele	0	1 (1.3%)
Hiatus hernia	0	1 (1.3%)
Esophageal food impaction	1 (2.9%)	0
Chest pain	0	1 (1.3%)
Non-cardiac chest pain	1 (2.9%)	0
Bacteremia	0	1 (1.3%)
Gastrointestinal viral infection	0	1 (1.3%)
Influenza	0	1 (1.3%)
Otitis media chronic	0	1 (1.3%)
Pneumonia	1 (2.9%)	0
Septic embolus	0	1 (1.3%)
Viral infection	0	1 (1.3%)
Fall	0	1 (1.3%)
Femur fracture	0	3 (3.9%)
Hand fracture	1 (2.9%)	
Lower limb fracture	1 (2.9%)	
Lumbar vertebral fracture	1 (2.9%)	
Tibia fracture	0	1 (1.3%)
Intraocular pressure increased	0	1 (1.3%)
Troponin T increased	1 (2.9%)	0
Urine protein/creatinine ratio increased	0	1 (1.3%)
Hyperkalemia	0	1 (1.3%)
Rhabdomyolysis	1 (2.9%)	4 (5.3%)
Vena cava thrombosis	0	1 (1.3%)

The Clinical Reviewer determined there were a number of SAEs in each treatment group that appear to be related to study procedures or to the patients' underlying condition of DMD.[8] However, one SAE of urine protein/creatinine ration increased, in the casimersen-treated group, may be related to casimersen. Kidney toxicity is discussed in section 5.1.

5.1 KIDNEY TOXICITY

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

Kidney toxicity is an identified risk for other antisense oligonucleotides including Viltepso (viltolarsen) which shares a similar molecular backbone with casimersen. Non-clinical toxicology studies showed signs of renal injury in casimersen-treated rodents and non-human primates. Five casimersen-treated patients experienced non-serious TEAEs possibly consistent with renal injury. Proteinuria occurred in all five patients with one also experiencing a SAE or urine protein/creatinine ratio increased. The Clinical Reviewer determined the non-clinical findings of renal toxicity may correlate with the clinical finding being that only casimersen-treated patients experiences these adverse events.[8] The labeling for casimersen will include kidney toxicity in the Warnings and Precautions with recommendations to monitor kidney function. Because creatinine may not be a reliable measure of renal function in patients with DMD, the label recommends the following:[11]

- Before starting casimersen:
  - Measure serum cystatin C, urine dipstick, and urine protein-to-creatinine ratio
  - Consider measuring glomerular filtration rate using an exogenous filtration marker
- During treatment with casimersen:
  - Monitor urine dipstick every month
  - Monitor serum cystatin C and urine protein-to-creatinine ratio every 3 months

5.2 DEATHS

During Study 4045-301, one death occurred with SAEs of cardiac arrest, hyperkalemia, and rhabdomyolysis. The SAEs transpired directly after the patient underwent surgical placement of a central venous port under sevoflurane general anesthesia, with additional IV fentanyl and propofol. Literature suggests it is known that patients with DMD undergoing medical procedures are at risk for potentially fatal reactions to inhaled anesthetics.[12] Specifically, sevoflurane, desflurane, isoflurane, and halothane have resulted in rhabdomyolysis in patients with DMD.[3] Such episodes can cause hyperkalemia and sudden death from cardiac arrest.[12] Thus, both the study investigator and the clinical reviewer agreed the SAEs were a complication of the surgical procedure, in combination with the underlying condition of DMD.[8]

6 Expected Postmarket Use

Casimersen will be prescribed and administered in the inpatient and outpatient setting. The likely prescribers include neurologists and primary care providers who are familiar with managing patients with DMD. These prescribers should be familiar with managing the adverse effects associated with casimersen and other antisense oligonucleotides, including kidney toxicity.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities beyond labeling and routine pharmacovigilance for casimersen. If approved, casimersen would be subject to postmarketing requirements including a confirmatory study.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends accelerated approval of casimersen considering the potential benefit of increased dystrophin production and the manageable risks of casimersen including kidney toxicity.

DMD is an inherited, X-linked recessive disease with significant morbidity and mortality. DMD primarily affects males and occurs in approximately 16 live male births per 100,000 in the U.S. Symptoms present in early childhood and affect activities of daily living, especially ambulation. Gradual deterioration occurs and most patients require noninvasive ventilation by late-teenage years. Survival beyond the third decade is uncommon.

There is no cure for DMD, however, there are four FDA-approved treatments for DMD (deflazacort, eteplirsen, golodirsen, and viltolarsen). Casimersen offers an additional agent for DMD patients with a confirmed mutation of the DMD gene that is amenable to exon 45 skipping.

Kidney toxicity is a potential risk associated with casimersen. Non-clinical studies showed signs of renal injury and clinical studies showed casimersen-treated patients experienced non-serious TEAEs possibly consistent with renal injury. The likely prescribers of casimersen, neurologists and primary care providers who treat patients with DMD, should be familiar with managing the adverse effects associated with casimersen and other antisense oligonucleotides, including potential kidney toxicity. Additionally, kidney toxicity will be included in the Warning and Precautions section of the label with monitoring recommendations. This reviewer recommends that, should casimersen be approved, a REMS is not necessary to ensure its benefits outweigh its risk.

9 Conclusion & Recommendations

Based on the available data, a REMS is not necessary for casimersen to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 References

1. Sarepta Therapeutics Inc. Amondys 45 (casimersen). NDA 213026. Prescribing Information, draft. June 25, 2020.
2. Duchenne muscular dystrophy. National Center for Advancing Translational Sciences. Genetic and Rare Diseases Information Center. https://rarediseases.info.nih.gov/diseases/6291/duchenne-muscular-dystrophy. Published November 2, 2020. Accessed November 12, 2020.
3. Darras BT. Duchenne and Becker muscular dystrophy: Management and prognosis. *UpToDate.* July 24, 2020.
4. Darras BT. Duchenne and Becker muscular dystrophy: Glucocorticoid and disease-modifying treatment. *UpToDate.* September 1, 2020.

5. Emflaza (deflazacort). Facts & Comparisons eAnswers. Wolters Kluwer Health, Inc. http://fco.factsandcomparisons.com/lco/action/doc/retrieve/docid/fc_dfc/6439003?cesid=abqb0wX0PYf&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Ddeflazacort%26t%3Dname%26va%3Ddeflazacort%26nq%3Dtrue. Accessed January 12, 2021.
6. U.S. Food and Drug Administration. Accelerated Approval. https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval. Published January 4, 2018. Accessed January 25, 2021.
7. Sarepta Therapeutics Inc. Amondys 45 (casimersen). NDA 213026. Module 2.7.3 - Summary of Clinical Efficacy. June 25, 2020.
8. Hosford D. Food and Drug Administration. Division of Neurology 1. Amondys 45 (casimersen). NDA 213026. Clinical Review, draft. January 4, 2021.
9. Sarepta Therapeutics Inc. Amondys 45 (casimersen). NDA 213026. Module 2.5 - Clinical Overview. June 25, 2020.
10. Sarepta Therapeutics Inc. Amondys 45 (casimersen). NDA 213026. Module 2.7.4 - Summary of Clinical Safety. June 25, 2020.
11. Sarepta Therapeutics Inc. Amondys 45 (casimersen). NDA 213026. Prescribing Information, draft. February 8, 2021.
12. Birnkrant DJ, Panitch HB, Benditt JO, et al. American College of Chest Physicians consensus statement on the respiratory and related management of patients with Duchenne muscular dystrophy undergoing anesthesia or sedation. *Chest*. 2007;132(6):1977-1986.

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