NEW DRUG APPROVAL

Brand Name	Amondys 45™
Generic Name	casimersen
Drug Manufacturer	Sarepta Therapeutics, Inc.

New Drug Approval

FDA Approval Date: February 25, 2021

Review Designation: Fast Track, Priority Review, Orphan Drug

Type of Review: New Drug Application (NDA): 213026

Dispensing Restriction(s): Limited Distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Duchenne muscular dystrophy (DMD) is a genetic disorder characterized by progressive muscle degeneration and weakness due to the alterations of a protein called dystrophin that helps keep muscle cells intact. DMD is one of four conditions known as dystrophinopathies. The other three diseases that belong to this group are Becker Muscular dystrophy (BMD, a mild form of DMD); an intermediate clinical presentation between DMD and BMD; and DMD-associated dilated cardiomyopathy (heart-disease) with little or no clinical skeletal, or voluntary, muscle disease.

DMD is the most common childhood onset form of muscular dystrophy and affects males almost exclusively. The birth prevalence is estimated to be 1 in every 3,500 live male births. Age of onset is usually between 3 and 5 years of age. The muscular dystrophies as a whole are estimated to affect 250,000 individuals in the United States.

Efficacy

Study 1 (NCT02500381) is an ongoing, double-blind, placebo-controlled, multicenter study designed to evaluate the safety and efficacy of Amondys 45™ in ambulatory patients. Patients of age 7 to 13 years randomized to Amondys 45™ or placebo in a 2 to 1 ratio. Patients were required to have been on a stable dose of oral corticosteroids for at least 24 weeks prior to dosing with Amondys 45™ or placebo. Interim efficacy was assessed based on change from baseline in the dystrophin protein level (measured as % of the dystrophin level in healthy subjects, i.e., % of normal) at Week 48 of Study 1. Interim results from 43 evaluable patients (n = 27, Amondys 45™; n = 16, placebo) who had a muscle biopsy at Week 48 of the double-blind period are presented in below screenshot. Patients who provided muscle biopsy data had a median age of 9 years and were 86% White. Patients who received Amondys 45™ showed a significantly greater increase in dystrophin protein levels from baseline to Week 48 of treatment compared to those who received placebo.

Table 2. Dystrophin Levels (% of Normal) at Baseline and at Week 48 from Muscle Biopsy Interim Results in Study 1

	Placebo	AMONDYS 45 30 mg/kg/week IV
Dystrophin by Sarepta Western blot	n=16	n=27
Baseline Mean (SD)	0.54 (0.79)	0.93 (1.67)
Week 48 Mean (SD)	0.76 (1.15)	1.74 (1.97)
Change from Baseline Mean (SD)	0.22 (0.49)	0.81 (0.70)
p-value Change from Baseline to Week 48	0.09	<0.001
Between group mean difference	0.59	
p-value between groups	p=0.004	

Safety

ADVERSE EVENTS

The most common adverse reactions (incidence >20% and at least 5% higher than placebo) were upper respiratory tract infection, cough, pyrexia, headache, arthralgia, and oropharyngeal pain. Other adverse reactions that occurred in at least 10% of patients treated with Amondys 45™, and that were reported at a rate at least 5% more frequently in the Amondys 45™ group than in the placebo group, were: ear pain, nausea, ear infection, post-traumatic pain, and dizziness and light-headedness.

WARNINGS & PRECAUTIONS

Kidney Toxicity: Kidney function should be monitored in patients taking Amondys 45™. During treatment, monitor urine dipstick every month, and serum cystatin C and urine protein-to-creatinine ratio (UPCR) every three months.

CONTRAINDICATIONS

None.

Clinical Pharmacology

MECHANISMS OF ACTION

Casimersen is designed to bind to exon 45 of dystrophin pre-mRNA resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 45 skipping. Exon 45 skipping is intended to allow for production of an internally truncated dystrophin protein in patients with genetic mutations that are amenable to exon 45 skipping.

Dose & Administration

ADULTS

30 mg/kg via IV infusion over 35 to 60 minutes once weekly via an in-line 0.2 micron filter.

PEDIATRICS

Refer to adult dosing.

GERIATRICS

DMD is largely a disease of children and young adults; therefore, there is no experience with Amondys 45™ in geriatric DMD patients.

RENAL IMPAIRMENT

Monitor renal function in all patients; specific guidelines for dosage adjustments in renal impairment are not available.

HEPATIC IMPAIRMENT

Specific guidelines for dosage adjustments in hepatic impairment are not available; it appears that no dosage adjustments are needed. Casimersen has not been studied in patients with hepatic impairment.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: 100 mg/2 mL in a single-dose vial.