New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Amondys 45® (casimersen) [Sarepta Therapeutics]**
Dosage Formulations:	injection for intravenous infusion, supplied in single dose vials containing 100 mg/2 mL
FDA Approval Date: **FDB File Date:**	FDA: February 25, 2021 FDB: March 7, 2021
Indication:	Treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping
Mechanism of Action:	Antisense oligonucleotide designed to bind to exon 45 of dystrophin pre-mRNA which results in the exclusion of this exon during mRNA processing.
Dose/ Administration:	30 mg/kg once weekly intravenous (IV) infusion over 35 to 60 minutes

Disease State Clinical Highlights:	• DMD is a fatal X-linked genetic disorder resulting from absent or defective dystrophin protein. Dystrophin levels of affected patients are usually less than 3% of normal; dystrophin is needed for normal muscle maintenance and function. DMD results in progressive and irreversible loss of muscle function.
	• The amount of dystrophin needed for functional improvement is currently unknown.
	  ○ Results from a study on mdx mice revealed the level of dystrophin needed for normal neuromuscular function is between 19 and 50%.
	  ○ Another study on mdx mice revealed that levels of dystrophin needed to improve muscle function were as low as 5 to 15%.
	  ○ An analysis of female carriers of DMD revealed that asymptomatic carriers had 50 to 65% of normal dystrophin protein levels, while those with less than 50% of normal levels display clear symptoms of muscle weakness.
	• DMD almost exclusively affects males. Females can be carriers; it is extremely rare for a female to inherit two affected X chromosomes.
	• DMD occurs in about 1 out of every 3,600 male infants worldwide. The prevalence of DMD is estimated to be about 6 per 100,000 individuals (15,000 – 20,000 people in the United States) or 1 in 3,500 – 5,000 live male births (400 – 600 boys per year in the United States).
	• Most patients with DMD require the use of a wheelchair by age 12, breathing support by age 20, and die by age 30, usually due to cardiac or respiratory failure.
	• Historically, standard of care for DMD has been management of symptoms.
	  ○ Use of glucocorticoids for neuromuscular symptoms.
	  ○ Physical and occupational therapy
	  ○ Surgery to improve gait in select patients
	  ○ Standard heart failure treatment for deterioration of cardiac function
	  ○ Initiation of ACE/ARB by age 10 years
	  ○ Bisphosphonates for bone fragility
	  ○ Gastrostomy placement for severe dysphagia
	  ○ Lung volume recruitment therapy for FVC <60%
	  ○ Ventilation/cough assistance for hypoxemia

Drug Clinical Highlights:	• Amondys 45 is the fourth antisense oligonucleotide for DMD approved via the accelerated approval pathway following Exondys 51®, Vyondys 53®, and Viltepso®, but the first specifically targeted for the DMD gene that is amenable to exon 45 skipping. • The FDA granted this application Fast Track and Priority Review designations. Amondys 45 also received Orphan Drug designation. • The FDA approved Amondys 45 based on interim efficacy at Week 48 of the Phase 3 ESSENCE trial, which is still ongoing and expected to conclude in 2024. • ESSENCE is a global, double-blind, randomized, placebo-controlled trial in which 43 male patients between ages 7 and 13 who have a confirmed mutation of the DMD gene

amenable to exon 45 skipping were randomized 2:1 to receive either placebo or Amondys 45 (30 mg/kg) via IV infusion every week for up to 96 weeks.

- Following the 96-week double-blind period, all patients began, or will begin, an additional 48-week open-label treatment period.
- Interim results at week 48:

Dystrophin Levels (% of Normal) at Baseline and at Week 48 from Muscle Biopsy: Interim Results		
	Placebo	**Amondys 45**
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	0.004	

- The patients who received Amondys 45 showed a statistically greater increase in dystrophin protein levels in skeletal muscle compared to patients on placebo (*P* = 0.004).
- The most common side effects observed in ≥ 20% of patients treated with Amondys 45 and 5% more frequently than in the placebo group were upper respiratory infection, cough, fever, headache, joint pain, and throat 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 than in the placebo group, were ear pain, nausea, ear infection, post-traumatic pain, dizziness and light-headedness.
- **Warning of potential kidney toxicity:** Based on animal data, Amondys 45 may cause kidney toxicity. Kidney function should be monitored; creatinine may not be a reliable measure of renal function in patients with DMD because of the effect of reduced skeletal muscle mass on creatinine measurements. Serum cystatin C, urine dipstick, and urine protein-to-creatinine ratio should be measured before starting Amondys 45.

Price Per Unit (WAC):

Annual cost for 30-kg person: $748,800
WAC = $800/mL and a 30-kg person will require 18 mL (9 single dose vials) per week

Therapeutic Alternatives:

- Amondys 45 is the only drug approved for the treatment of DMD in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 45 skipping.
- Vyondys 53 and Viltepso are approved for the treatment of DMD in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 53 skipping.
- Exondys 51 is approved for the treatment of DMD in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 51 skipping.
- Emflaza® (deflazacort) is a glucocorticoid indicated for the treatment of DMD in patients two years of age and older.
- Prednisone (off-label) is recommended by American Academy of Neurology (AAN) guidelines for the treatment of DMD – high quality studies have shown benefit

Medication	WAC/year (30 kg child)
Amondys 45	$748,000.00
Exondys 51	$748,000.00
Viltepso	$733,200.00
Vyondys 53	$748,000.00
Emflaza tablet	$90,627.68
Emflaza suspension	$122,469.18
Prednisone tablet	$114.98

Prior Authorization Approval Criteria:	**Must meet the following criteria:**
	
	Initial Therapy:
	• Documented diagnosis of DMD confirmed by:
	  ○ Genetic testing for dystrophin gene deletion or duplication **OR**
	  ○ Genetic sequencing screening for pathogenic variant attributed to DMD **OR**
	  ○ Positive muscle biopsy showing absence of dystrophin protein **AND**
	• Genetic testing to confirm pathogenic variant of *DMD* gene amenable to exon 45 skipping **AND**
	• Prescribed by or in consultation with a neurologist or other appropriate specialist **AND**
	• Age > 7 to < 13 years based on clinical study inclusion criteria **AND**
	• Documentation of baseline serum cystatin C, urine dipstick, and urine protein-to-creatinine ratio (UPCR) **AND**
	• Documentation of baseline clinical criteria [ex: ambulatory status, 6-minute walk test (6MWT), Ejection Fraction, North Star Ambulatory Assessment (NSAA), Brooke Upper Extremity Function Scale, Forced vital capacity (FVC)] **AND**
	• Maximum dosing of 30 mg/kg infused once weekly **AND**
	• Documentation of concurrent prednisone or deflazacort therapy, defined as at least 6 months in the past 9 months **AND**
	• Initial approval: 6 months
	
	Continuation of Therapy:
	• Improvement, stabilization or less than expected decline of disease progression of motor, pulmonary or cardiac function from baseline (ex: 6MWT, NSAA, Brooke Upper Extremity Scare, FVC, Ejection Fraction) **AND**
	• Participant retains meaningful voluntary motor function (ex: able to speak, manipulate objects using upper extremities, ambulate) **AND**
	• Renal function monitoring (documentation of appropriate monitoring of renal function ex: urine dipstick monthly, serum cystatin C and urine protein-to-creatinine ratio every three months)
	• Reauthorization: 6 months

Implication to State Medicaid Program:	LOE Date: TBD • Sarepta's pipeline for DMD includes line extension products for their 3 exon-skipping drugs, using a peptide-conjugated phosphorodiamidate morpholino oligomer (PPMO) platform version to extend their dosing intervals. • One of these drugs is SRP-5051, which offers the potential for improved efficacy (as far as the endpoint of the surrogate marker of muscle dystrophin) with less frequent dosing. With total dose exposure ~10 times lower than Exondys 51, SRP-5051 is dosed once a month and, in the Phase 2 MOMENTUM clinical trial (NCT04004065), showed a 1.6-fold increase in exon skipping and a 5-fold increase in the percentage of normal dystrophin when compared to Exondys 51. However, as it is still unknown whether these exon-skipping products provide any clinical benefit, these next-generation exon-skipping products will continue to be controversial. Phase III Trials • Translarna™ (ataluren) [PTC Therapeutics]: oral inhibitor of premature protein translation termination • ITF2357 (givinostat) [Italfarmaco]: oral histone deacetylase (HDAC) inhibitor • FG-3019 (pamrevlumab) [FibroGen]: IV anti-CTGF antibody • PF-06939926 (TBD) [Pfizer]: IV gene therapy • Raxone (idebenone) [Santhera]: oral synthetic short-chain benzoquinone

References:

1. AMONDYS 45 (casimersen) [package insert]. Cambridge, MA: Sarepta Therapeutics; February 2021
2. VILTEPSO (viltolarsen) [package insert]. Paramus, NJ: NS Pharma, Inc.; August 2020.
3. VYONDYS 53 (golodirsen) [package insert]. Cambridge, MA: Sarepta Therapeutics, Inc.; August 2020.
4. EXONDYS 51 (eteplirsen) [package insert]. Cambridge, MA: Sarepta Therapeutics, Inc.; September 2016.
5. IPD Analytics Rx Insights_New Drug Review: Amondys. Accessed April 4, 2021.
6. Institute for Clinical and Economic Review (ICER). Final Evidence Report on Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy: Effectiveness and Value. Published August 15, 2019. Accessed April 5, 2021. https://icer.org/wp-content/uploads/2020/10/ICER_DMD-Final-Report_081519-2-1.pdf
7. National Institutes of Health, Genetic and Rare Diseases Information Center. Duchenne muscular dystrophy. Updated November 2, 2020. Accessed April 5, 2021. https://rarediseases.info.nih.gov/diseases/6291/duchenne-muscular-dystrophy