GENE AND CELLULAR THERAPY - Exon Skipping Agents

Casimersen (Amondys 45; Sarepta Therapeutics, Inc.)
FDA Approval Date: 02/25/2021

AHFS PHARMACOLOGIC THERAPEUTIC CLASS
92:18 - Antisense Oligonucleotides
LEXI-COMP PHARMACOLOGIC THERAPEUTIC CLASS
Antisense Oligonucleotide

CURRENT FORMULARY STATUS WITHIN ENTERPRISE
Formulary

AVAILABLE FORMULATIONS[1]

- Solution, Intravenous [preservative free]
    - Single-dose vials containing 100 mg/2 mL (50 mg/mL)

INDICATIONS[12]

FDA Approved

- Treatment of Duchenne muscular dystrophy (DMD) in patients who have confirmed mutation of the DMD gene that is amenable to exon 45 skipping.
- Of note, Amondys 45 was approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients.

Off-Label uses

- None

DESCRIPTION AND CLINICAL PHARMACOLOGY[23]

Casimersen binds 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 produces an internally truncated dystrophin protein.

PHARMACODYNAMICS AND PHARMACOKINETICS[3]

Distribution	V_{dss}: 367 mL/kg
Protein binding	8.4% to 31.6%
Half-life elimination	3.5 hours
Excretion	Urine: >90% as unchanged drug

DOSING AND ADMINISTRATION[1]

Indication	Dosing
DMD - Adult	IV: 30 mg/kg/dose once weekly.
DMD - Pediatric	

Geriatric

- Refer to adult dosing.

Renal impairment

- There are no dosage adjustments provided in the manufacturer's labeling.
- Monitor closely.

Hepatic impairment

- Has not been studied - There are no dosage adjustments provided in the manufacturer's labeling.

LITERATURE REVIEW AND CLINICAL EFFICACY[24]

In the interim efficacy analysis at week 48 of the phase 3 ESSENCE study, the Amondys 45 arm demonstrated an increase in mean dystrophin protein (% normal dystrophin as measured by western blot) to 1.736% of normal compared to a mean baseline of 0.925% and a significant difference in the mean change from baseline to week 48 in dystrophin protein compared to placebo. Of the patients who have been tested for increased exon-skipping mRNA using reverse transcription polymerase chain reaction (RT-PCR), all displayed an increase in skipping exon 45 over their baseline levels, representing a 100% response rate. A positive correlation between exon 45 skipping and dystrophin production was observed. The study is ongoing and remains blinded to collect additional efficacy and safety data. It is expected to conclude in 2024 as the confirmatory trial for Amondys 45 and Vyondys 53.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS[23]

Black Boxed Warnings

- N/A

Contraindications

- There are no contraindications listed in the manufacturer's labeling.

Warnings and Precautions

- Renal impairment
    - Renal clearance is reduced in non-Duchenne muscular dystrophy (DMD) patients with renal impairment; however, creatinine is not a reliable measurement of kidney function in patients with DMD due to reduced muscle mass.
    - Based on animal data, Amondys 45 may cause kidney toxicity. Kidney function should be monitored.

ADVERSE REACTIONS[5]

Common

- Gastrointestinal: Pain in throat (21%)
- Musculoskeletal: Arthralgia (21%)
- Neurologic: Headache (32%)
- Respiratory: Cough (33%), Upper respiratory infection
- Other: Fever (33%)

Serious

- None

RISK EVALUATION AND MITIGATION STRATEGIES

There is no REMS program associated with Amondys 45.

MAJOR INTERACTIONS

Drug-Drug[1]

- There are no known significant interactions.

Drug-Disease[3]

- May interfere with detection of urine protein (false positive) when pyrogallol red reagent is used.
    - Use a lab test that does not contain this reagent or use urine free of casimersen.
        - E.g. urine obtained prior to infusion or ≥48 hours after infusion.

MONITORING REQUIREMENTS[1]

- Proteinuria by dipstick urinalysis - baseline and monthly
- Serum cystatin C and urine protein-to-creatinine ratio - baseline and every 3 months
- GFR using an exogenous filtration marker - baseline
- Hypersensitivity reactions - during infusion

PREGNANCY/BREASTFEEDING[1]

- DMD primarily affects males; animal reproduction studies have not been conducted and females were not included in studies.
- It is not known if casimersen is present in breast milk.

MEDICATION SAFETY ISSUES[1]

Sound/Look Alike issues

- N/A

High Alert Medication

- N/A

SPECIAL STORAGE PRECAUTIONS[3]

- Store at 2 to 8°C (36 to 46°F) in the original carton to protect from light.
- Do not freeze.
- Diluted solution may be stored for up to 24 hours at 2 to 8°C (36 to 46°F)
- Stable for 4 hours at room temperature.

SPECIAL HANDLING/ADMINISTRATION[3]

- Allow vials to warm to room temperature prior to dilution. Mix contents of each vial by gently inverting 2 or 3 times; do not shake.
- Use a 21-gauge or smaller or non-coring needle to withdraw the calculated volume and dilute in NS to a total volume of 100 to 150 mL.
- Do not use if the solution in vial is cloudy, discolored, or contains extraneous particulate matter other than trace amounts of small, white to off-white, amorphous particles.
- Administer by IV infusion over 35 to 60 minutes through a 0.2-micron inline filter attached to the primary IV tubing: complete infusion within 4 hours of dilution.
- Discard unused portions.
- Use of a topical anesthetic cream on the infusion site may be considered prior to administration.
- Flush IV access line with NS prior to and after infusion.
- Do not mix with other medications or infuse other medications concomitantly via the same IV access line.

COST AND REIMBURSEMENT INFORMATION[26]

Cost (Estimated WAC)	Annual cost for 30-kg person: $748,800 (30 kg * 30 mg/kg per week = 90 mg weekly = 18 mL/week; WAC = 800/mL * 18 mL * 52 weeks)
Sales Projections (Estimated)	Analyst reports state expected peak annual sales of $227M in 2025.
Medical/Pharmacy Benefit	Medical
Inpatient/Outpatient	Outpatient
Reimbursement Code	NDC 60923-0227-02: Single-dose vials containing 100 mg/2 mL (50 mg/mL)
NOC Code Billing Guide	See IPD COSESOURxCE

HCPS	Billing Unit	GPO Cost /Billing Unit	340 B Cost/ Billing Unit	Medicare	Traditional WV Medicaid	Aetna Better Health	BCBS	PEIA
J1426	10 mg	N/A		Waiting for price				

Patient Assistance Availability	Pass Through Status	NTAP	Charge Map/ Method	Charge/ Rev Cod	Bill by	Allow billing for waste?
Yes	Yes	No	N/A	0636	Admin amount	Yes

PATIENT ASSISTANCE AVAILABILITY[7]

- SareptAssist by Sarepta Therapeutics, Inc. offers free or low-cost drugs to individuals who are unable to pay for their medication.
- Patients must meet financial and other program specific criteria to be eligible for assistance.
- Care managers provide information on insurance benefits, financial assistance options, treatment logistics, options for weekly infusions, and ongoing education and support.
- Additional information available at sarepta.com/sareptassistcall; 1-888-SAREPTA, M-F 8:30AM-6:30PM ET.

REFERENCES

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