GENE AND CELLULAR THERAPY - Exon Skipping Agents

Golodirsen (Vyondys 53; Sarepta Therapeutics, Inc.)
FDA Approval Date: 12/12/2019

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]: 100 mg/2 mL (2 mL)

INDICATIONS[1]
FDA Approved
- Treatment of Duchenne muscular dystrophy (DMD) in patients who have confirmed mutation of the DMD gene that is amenable to exon 53 skipping.

Off-Label uses
- None

DESCRIPTION AND CLINICAL PHARMACOLOGY[1]
Vyondys 53 binds to exon 53 of dystrophin pre-messenger RNA (mRNA), excluding this exon during processing. Exon 53 skipping allows for production of an internally truncated dystrophin protein in patients with genetic mutations that are amenable to exon 53 skipping.

PHARMACODYNAMICS AND PHARMACOKINETICS[1]

Distribution	V_{dss}: 0.67 L/kg
Protein binding	Plasma: 33 to 39%
Half-life elimination	3.4 hours
Excretion	Urine (mostly unchanged)

DOSING AND ADMINISTRATION[1]

Indication	Dosing
DMD	IV: 30 mg/kg once weekly

Geriatric
- Refer to adult dosing.

Pediatric
- Determine serum cystatin C, urine dipstick (proteinuria), and urine protein-to-creatinine prior to therapy; also consider baseline GFR using an exogenous filtration marker.

- Children and adolescents: refer to adult dosing. Dosing based on clinical trials in pediatric patients aged 6 to 13 years at study entry.

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[2,3]

In the interim efficacy analysis of the phase 3 ESSENCE study, the Vyondys 53 arm demonstrated a mean increase in truncated dystrophin quantification by western blot relative dystrophin levels from 0.1% of normal at baseline to 1.02% after 48-59 weeks, with a mean change of 0.92% ($p < 0.001$). The most frequent adverse events were headache, pyrexia, and gastrointestinal symptoms. 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[4]

Black Box Warnings

- N/A

Contraindications

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

Warnings and Precautions

- Hypersensitivity reactions
    - Including rash, pyrexia, pruritus, urticaria, dermatitis, and skin exfoliation.
    - Manage appropriately and consider slowing the infusion or interrupting therapy.
- Kidney toxicity
    - Including potentially fatal glomerulonephritis have been observed with some antisense oligonucleotides.
    - Creatinine may not be a reliable measure of kidney function in patients with DMD. Refer to a nephrologist if persistent increases in serum cystatin C or proteinuria occur.

ADVERSE REACTIONS[5]

Common

- Gastrointestinal: Abdominal pain (27%), Constipation (>5%), Nasopharyngitis (27%), Nausea (20%), Vomiting (27%)
- Musculoskeletal: Falling injury (29%)
- Neurologic: Headache (41%)
- Respiratory: Cough (27%)
- Other: Fever (41%)

Serious

- Immunologic: Hypersensitivity reaction
- Renal: Glomerulonephritis

Dose Adjustments for Toxicity

- Hypersensitivity reactions
    - Consider slowing infusion or interrupting therapy.

RISK EVALUATION AND MITIGATION STRATEGIES
There is no REMS program associated with Vyondys 53.

MAJOR INTERACTIONS[4]
Drug-Drug
- There are no known significant interactions.

Drug-Disease
- May interfere with detection of urine protein (false positive) when pyrogallol red reagent is used.
    - Use a laboratory test that does not contain pyrogallol red reagent or use urine free of Vyondys 53 (e.g. urine obtained prior to infusion or ≥ 48 hours after infusion).n significant drug interactions.

MONITORING REQUIREMENTS[1]
- Proteinuria by dipstick urinalysis baseline and monthly.
- Serum cystatin C and urine protein-to-creatinine ratio baseline and every 3 months.
- Urine samples should be obtained prior to infusion or at least 48 hours after the most recent infusion. Use laboratory tests that do not use reagent pyrogallol red - may cross react with golodirsen leading to false positive.
- GFR using an exogenous filtration marker at baseline.
- Hypersensitivity reactions during infusion.
- Kidney toxicity.

PREGNANCY/BREASTFEEDING[1]
- Vyondys 53 has not been studied in females. Animal reproduction studies have not been conducted.
- It is not known if Vyondys 53 is present in breast milk.

MEDICATION SAFETY ISSUES[1]
Sound/Look Alike issues
- Golodirsen may be confused with Goldenseal, Golden Seal, gold sodium thiomalate.

High Alert Medication
- None

SPECIAL STORAGE PRECAUTIONS[4]
- Store at 2 to 8°C (36 to 46°F). Do not freeze. Protect from light and store in the original carton until ready to use.
- The diluted solution may be stored at 2 to 8°C (36 to 46°F) for up to 24 hours.

SPECIAL HANDLING/ADMINISTRATION[4]
- Calculate patient-specific dose and determine number of vials needed.
- 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, low protein binding, inline filter attached to the primary IV tubing: complete infusion within 4 hours of dilution.
- Consider slowing the infusion or interrupting therapy for hypersensitivity reactions.
- Flush IV access line with NS prior to and after infusion.
- May consider application of a topical anesthetic cream to the infusion site prior to administration.
- Do not mix with other medications or infuse other medications concomitantly via the same IV access line.
- If a dose is missed, administer as soon as possible after the scheduled time.

COST AND REIMBURSEMENT INFORMATION[2,6]

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 $300M in 2025.
Medical/Pharmacy Benefit	Medical
Inpatient/Outpatient	Outpatient, hospital, physician office, home infusion
Reimbursement Code	NDC 60923-0465-02; Single-dose vials containing 100 mg (50 mg/mL) 2 mL
NOC Code Billing Guide	NOC: J3490, J3590, or C9399 (See IPD CodeSource)

HCPS	Billing Unit	GPO Cost /Billing Unit	340 B Cost/ Billing Unit	Medicare	Traditional WV Medicaid	Aetna Better Health	BCBS	PEIA
J1429	10 mg	$160.00	$120.62	$80.64-$155.51 No ASP established	$80.64-$155.51	$86.28-$166.41	Not covered	$80.64-$155.51 Not listed on formulary

Patient Assistance Availability	Pass Through Status	NTAP	Charge Map/ Method	Charge/ Rev Cod	Bill by	Allow billing for waste?
Yes	Yes	No	IV charges over $1,000 Cost x 1.8	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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