Drug Monograph

Drug Name: **Vyondys 53™ (golodirsen) injection**
Drug Class: **Oligonucleotide Agent**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Vyondys 53 is available in a single-dose vial as a 100 mg/2 ml preservative-free intravenous solution.
Manufacturer:	Manufactured for: Sarepta Therapeutics, Inc. Cambridge, MA 02142
Summary of Findings:	Vyondys 53 is the first exon-skipping, disease-modifying treatment for Duchenne muscular dystrophy (DMD) specifically designed to treat the subset of DMD patients amenable to skipping exon 53. It was approved under the FDA's accelerated approval program due to the increase in skipping of exon 53 and in dystrophin in a 2-part trial consisting of a randomized, double-blinded, placebo-controlled study and an open-label efficacy and safety study. In Part 1, patients were randomized to an increasing, titrating dose of Vyondys 53 or placebo, while in Part 2, patients all received a 30 mg/kg intravenous infusion weekly. After treatment with Vyondys 53, all patients evaluated in Trial 1, Part 1 had an increase in skipping of exon 53 compared to baseline. The mean change from baseline in dystrophin after treatment with Vyondys 53 was 0.92% (SD 1.01) of normal levels ($p<0.001$); the median change from baseline was 0.88%.
Status Recommendation:	☒ Clinical Edit ☐ Open Access ☐ PA Required ☐ PDL
Type of PA Criteria:	☒ Appropriate Indications ☐ No PA Required ☐ Non-Preferred ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

Duchenne muscular dystrophy (DMD) is an inherited progressive myopathic disorder. It is caused by mutations of the dystrophin gene that are inherited as an X-linked recessive trait. In some cases of DMD, a mutation in the X chromosome gene that encodes for dystrophin, a protein involved in muscle integrity, occurs. Thus, exons, sections of a DNA or RNA molecule that hold coding information for protein synthesis, can end up being deleted and ultimately interfere with the genetic code. This interference can halt protein production so that no dystrophin protein can be produced by the muscle cells. Without dystrophin, the muscle's integrity is lost and it can become easily damaged making progressive muscle weakness the principal symptom as the muscle fibers degenerate. In DMD patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping, Vyondys 53 can bind to exon 53 of dystrophin mRNA in the affected gene and essentially mask it, allowing this exon to be skipped and other exons to make a smaller, but functional, dystrophin protein. Other symptoms of DMD include elevated muscle enzymes such as serum creatinine kinase (CK) during early childhood, growth delay, orthopedic complications, and cognitive and behavioral disorders with patients usually becoming wheelchair-bound by age 12 to 13. Patients with DMD often die in their late teens or twenties due to respiratory insufficiency and cardiomyopathy. Clinical onset of muscle weakness usually starts between the ages of two and three but diagnosis can take place with any evidence of delayed motor milestones in young children with a family history positive for DMD. DMD typically manifests clinically in male patients, but in rare instances, female carriers of DMD mutations can exhibit similar progressive symptoms. Studies from Europe and North America have estimated the prevalence of DMD ranges from 1.3 to 2.1 per 10,000 live male births. It is also estimated that about 8% of boys with DMD may be amenable to exon 53 skipping.

Dosage Form [3]

Vyondys 53 is available in a single-dose vial as a 100 mg/2 ml preservative-free intravenous solution.

Manufacturer [3]

Manufactured for: Sarepta Therapeutics, Inc. Cambridge, MA 02142

Indication(s) [3]

Vyondys 53 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with Vyondys 53. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

Clinical Efficacy [3,4,5] (mechanism of action/pharmacology, comparative efficacy)

Vyondus 53 is an antisense oligonucleotide that binds to exon 53 of dystrophin pre-mRNA, resulting in the exclusion of this exon during mRNA processing in DMD patients with genetic mutations that are amenable to exon 53 skipping. Exon 53 skipping is intended to allow for the production of an internally truncated dystrophin protein in patients with genetic mutations that are amenable to exon 53 skipping.

Pharmacokinetics:

Protein Binding	Plasma: 33 to 39%
Volume of Distribution	0.67 L/kg
Metabolism	Metabolically stable; no metabolites were detected in plasma or urine
Excretion	Urine: mostly unchanged
Half-life	3.4 hours

Clinical Trials Experience

STUDY 1 DESIGN	Trial 1 was a 2-part multicenter study consisting of: Part 1: a randomized, double-blind, parallel-assignment, placebo-controlled, dose-titration, safety, tolerability, and pharmacokinetics study (n = 12); and, Part 2 was an open-label efficacy and safety evaluation (n = 25)
INCLUSION CRITERIA	• Diagnosis with DMD, genotypically confirmed • Intact right and left biceps muscles or an alternative upper arm muscle group • Stable pulmonary and cardiac function • Minimum performance on 6-Minute Walk Test (6MWT), North Star Ambulatory Assessment, and rise (Gowers) test as specified in the study protocol • On a stable dose of corticosteroids for at least 6 months
EXCLUSION CRITERIA	• Previous treatment with the experimental agents Ezutromid (BMN-195) or PRO053 • Current or previous treatment with any other experimental treatments within 12 weeks prior to study entry • Major surgery within the last 3 months • Presence of other clinically significant illness • Major change in the physical therapy regime within the last 3 months

TREATMENT REGIMEN	Trial 1, Part 1: Patients were randomized to receive 4 mg/kg weekly on weeks 1-2; 10 mg/kg weekly on weeks 3-4; 20 mg/kg weekly on weeks 5-6; and 30 mg/kg weekly on weeks 7-12 Vyondys 53 or placebo-matching IV infusions for 12 weeks Trial 1, Part 2: Patients received Vyondys 53 30 mg/kg weekly for up to 168 weeks
RESULTS	The primary endpoints, according to *ClinicalTrials.gov*, were incidence of adverse events and serious adverse events during the 12-week long part 1, change in 6MWT from baseline in 48-week long part 2, and percentage of dystrophin-positive fibers in 48-week long part 2. The only set of primary endpoint measurements found were as follows: After treatment with Vyondys 53, all patients evaluated in Trial 1, Part 1 had an increase in skipping of exon 53 demonstrated by reverse transcription polymerase chain reaction (RT-PCR), compared to baseline. In Trial 1, Part 2, dystrophin levels increased from 0.10% (SD 0.07) of normal baseline to 1.02% (SD 1.03) of normal after 48 weeks of treatment with Vyondys 53. The mean change from baseline in dystrophin after 48 weeks of treatment with Vyondys 53 was 0.92% (SD 1.01) of normal levels ($p<0.001$); the median change from baseline was 0.88%. This increase in dystrophin protein expression positively correlated with the level of exon skipping.
SAFETY	Discussed in the Adverse Effects section below.

Contraindications [3,4]

- None

Warnings and Precautions [3,4]

- Hypersensitivity: hypersensitivity reactions have been reported with use; manage appropriately and consider slowing the infusion or interrupting therapy.
- Renal toxicity: renal toxicity, including potentially fatal glomerulonephritis, has been observed with some antisense oligonucleotides; monitor renal function at baseline and during treatment.
- Pregnancy: Animal reproduction studies or studies in females have not been conducted.
- Lactation: It is not known if Vyondys 53 is present in breast milk. Studies in females have not been conducted. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.

Adverse Effects [3,4]

Most common, ≥ 10 %	Vyondys 53 (n =) %	Placebo (n =21) %[a]
Headache	41	10
Pyrexia	41	14
Falling	29	19
Abdominal Pain	27	10
Nasopharyngitis	27	14
Cough	27	19
Vomiting	27	19
Nausea	20	10

a = number of patients in Adverse Effects table includes patients in Trial 1 and Trial 2, which are not included in the primary outcomes discussion patient numbers due to a lack of finalized results

Drug Interactions [3,4]

- There are no known significant drug interactions.

Dosage and Administration [3,4]

- Adult: 30 mg/kg intravenously once weekly.
- Adult, renal impairment: There are no dosage adjustments provided; monitor closely.
- Pediatric: 30 mg/kg intravenously once weekly.
- Pediatric, renal impairment: There are no dosage adjustments provided; monitor closely. Note that creatinine is not a reliable measurement of kidney function due to the reduced skeletal mass in patients with DMD.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**
Golodirsen	Vyondys 53	Sarepta	100 mg/2 mL	$800 per 2 mL vial

** Wholesale Acquisition Cost

Conclusion

Vyondys 53 is the second exon-skipping, disease-modifying FDA-approved treatment of DMD. It is the first, however, to treat the subset of DMD patients amenable to skipping exon 53, and it was approved under the FDA's accelerated approval program. Vyondys 53 works by binding to exon 53 of dystrophin pre-mRNA, resulting in the exclusion of this exon during mRNA processing in DMD patients with genetic mutations that are amenable to exon 53 skipping. This allows smaller, but functional, dystrophin proteins to be synthesized thus slowing down the progression of muscle weakness. The efficacy of Vyondys 53 was established in a 2-part trial consisting on a randomized, double-blind, placebo-controlled study. Treatment with Vyondys 53 demonstrated a significant reduction in mortality and frequency of cardiovascular-related hospitalizations. There are many known adverse reactions associated with Vyondys 53 use, but one should weigh the benefits of treatment against the risks.

Recommendation

The MO Healthnet Division recommends adding this drug to the rare disease clinical edit.

References

1) Darras, B. (2018). Duchenne and Becker muscular dystrophy: Clinical features and diagnosis. In J. F. Dashe (Ed.), UpToDate. Retrieved January 29, https://www.uptodate.com/contents/duchenne-and-becker-muscular-dystrophy-clinical-features-and-diagnosis
2) Iver, V. (2019, December 13). Vyondys 53 (Golodirsen). Retrieved January 30, 2020, from https://musculardystrophynews.com/golodirsen-srp-4053/
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4) Golodirsen: Drug Information. Lexi-Drugs. Wolters Kluwer Clinical Drug Information Inc.
5) ClinicalTrials.gov Identifier: NCT02310906. (n.d.). Phase I/II Study of SRP-4053 in DMD Patients – Full Text View. Retrieved January 30, 2020, from https://clinicaltrials.gov/ct2/show/NCT02310906
6) Muntoni, F., Frank, D., Morgan, J., Domingos, J., Schnell, F., Dickson, G., … Straub, V. (2018). Golodirsen induces exon skipping leading to sarcolemmal dystrophin expression in patients with genetic mutations amenable to exon 53 skipping. Neuromuscular Disorders, 28. Doi: 10.1016/s0960-8966(18)30304-3

Prepared by: Jo Klinger, PharmD
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