

POLICY: Muscular Dystrophy – Vyondys 53 (golodirsen intravenous infusion – Sarepta)

APPROVAL DATE: 12/13/2019

OVERVIEW

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.¹ Vyondys 53 was approved for this indication under accelerated approval based on an increase in dystrophin observed in the skeletal muscle of patients who received the drug. The prescribing information notes that continued FDA-approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.

Disease Overview

DMD is an X-linked recessive disease affecting 1 in 3,600 to 6,000 newborn male infants.² The disease is attributed to large frame-shift deletions in the DMD gene (chromosome Xp21) which lead to loss of a structural protein of muscle cells (dystrophin).³ Over 4,700 mutations on the DMD gene have been identified which lead to a deficiency in production of dystrophin.² Therefore, the type of mutation and its effect on the production of dystrophin accounts for the variable phenotypic expression.⁴ Females carriers are usually asymptomatic but some may show mild symptoms.² There are wide variances in how quickly DMD progresses, but without intervention death is at approximately 19 years of age.²⁻⁴ With respiratory, cardiac, orthopedic and rehabilitative interventions and use of corticosteroids, children born today can have a life expectancy of up to 40 years.

Vyondys 53 is an antisense oligonucleotide designed to bind to exon 53 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 53 skipping.¹ These patients represent up to 10% of all patients with DMD.⁵ This genetic manipulation intends to restore the reading frame of the resulting mRNA. The result would be production of a shortened, but partially functional dystrophin protein as seen in less severe forms of muscular dystrophy (e.g., Becker muscular dystrophy). Of note, the reading frame of certain deletions (e.g., exon 52 deletions) can be restored by skipping either exon 51 or exon 53.⁶ Approximately 8% of mutations are amenable to skipping exon 53 with Vyondys 53 but are not amenable to skipping of exon 51.

Guidelines

There are guidelines for the diagnosis and management of DMD available from the DMD Care Considerations Working Group (2018).⁴ Genetic testing for a DMD mutation in a blood sample is always required. By fully characterizing the mutation, the predicted effect on the reading frame can be identified, which is the major determinant of phenotype and will determine eligibility for mutation-specific clinical trials. In patients with no mutation identified but with signs/symptoms of DMD, a muscle biopsy is clinically indicated. Glucocorticoids slow decline in muscle strength and function in DMD. Use of corticosteroids reduces the risk of scoliosis and stabilizes pulmonary function. Continued treatment after the patient loses ambulation provides a reduction in the risk of progressive scoliosis and stabilization of pulmonary function tests. Therefore, glucocorticoids should be considered for all patients with DMD. Exondys 51 (eteplirsen intravenous infusion) is mentioned as an emerging product, approved by an accelerated pathway for those with a mutation in the dystrophin gene amenable to exon 51 skipping. However, these guidelines do not specifically address exon 53 skipping or mention Vyondys 53 in the guidelines.

POLICY STATEMENT

The prescribing information for Vyondys 53 states that approval is based on dystrophin production in a limited number of patients (n = 25) with DMD, but approval may be contingent upon a confirmatory trial. Due to inadequate clinical efficacy data, **approval is not recommended** for Vyondys 53.

RECOMMENDED AUTHORIZATION CRITERIA

None.

FDA-Approved Indications

Vyondys 53 has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

- 1. Duchenne Muscular Dystrophy (DMD).** Due to inadequate clinical efficacy data, approval is not recommended for Vyondys 53. A systemic review and meta-analysis of other exon skipping therapies (i.e., Exondys 51, drisapersen) does not show benefit of these therapies for DMD.⁹ The prescribing information notes that continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.¹ FDA has required a post-marketing trial to verify clinical efficacy of Vyondys 53.

The efficacy of Vyondys 53 was evaluated in one unpublished, open-label study in patients with DMD that is amenable to exon 53 skipping.^{1,7,8} Dystrophin protein at Week 48 and 6-minute walk test (6MWT) results at Week 144 were the primary clinical endpoints. Among the patients who received Vyondys 53 in Part 2 of the study (n = 25) the normal dystrophin protein increased from baseline (0.10%) through Week 48 (1.02%; P < 0.001). In individual patient biopsies at Week 48, the dystrophin level ranged from 0.09% to 4.3%, with a mean per-patient 16.0-fold increase in dystrophin. At Week 48, the mean level of exon 53 skipping increased to 18.6% (SD, 13.2%; range, 2.6% to 150.3%) vs. 2.6% (SD, 4.1%; range, 0.0 to 14.7%) at baseline. The percent dystrophin-positive fibers scoring increased from 1.4% (SD, 2.4%; range, 0.06% to 9.8%) at baseline to 10.5% (SD, 10.1%; range, 0.9% to 32.6%) [P < 0.001] at Week 48. There was a mean per-patient 13.5-fold increase in percent dystrophin-positive fibers from baseline through Week 48. 6MWT results have not yet been reported.

- 2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.**

REFERENCES

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9. Shimizu-Motohashi Y, Murakami T, Kimura E, et al. Exon skipping for Duchenne muscular dystrophy: a systematic review and meta-analysis. *Orphanet J Rare Dis*. 2018;13(1):93.

HISTORY

Type of Revisor	Summary of Changes	Date Reviewed
New Policy	--	12/13/2019