Drug Monograph

Drug/Drug Class:	**Exondys 51® (eteplirsen) injection/ Antisense Oligonucleotide Agent**
Prepared for:	MO HealthNet
Prepared by:	Xerox Heritage, LLC

☒ **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 & Manufacturer:	Exondys 51® is available in a single-dose vial for injection in strengths of 100 mg eteplirsen per 2 ml and 500 mg eteplirsen per 10 ml respectively. Manufacturer: Serepta Therapeutics, Inc., Cambridge, MA 02142
Summary of Findings:	Exondys 51® was evaluated in 3 clinical studies. The primary endpoints studied were dystrophin production and assessment of the 6 minute walk test. In the 3 trials, there was not a significant difference in change in the 6 minute walk test between patients treated with Exondys 51® and those treated with placebo. In the first 2 trials, it was not possible to estimate dystrophin production in response to Exondys 51® due to lack of information on dystrophin protein levels before treatment. In the final study, results showed a median increase of 0.1% in dystrophin levels after 48 weeks of treatment with Exondys 51®.
Status Recommendation:	☒ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☐ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☒ Appropriate Indications ☐ Non-Preferred Agent

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 [2]

Duchenne muscular dystrophy (DMD) is a rare genetic disorder characterized by progressive muscle deterioration and weakness. It is cause by an absence of dystrophin, a protein that helps keep muscle cells intact. The first symptoms are usually seen between 3 and 5 years of age, and worsen over time. People with Duchenne muscular dystrophy progressively lose the ability to perform activities independently and often require use of a wheelchair by their early teens. As the disease progresses, life-threatening heart and respiratory conditions can occur. Approximately 1 in every 3,600 male infants worldwide are affected by DMD.

Dosage Form(s) [1]

Exondys 51® is available in a single-dose vial for injection in strengths of 100 mg eteplirsen per 2 ml and 500 mg eteplirsen per 10 ml respectively.

Manufacturer [1]

Serepta Therapeutics, Inc., Cambridge, MA 02142

Indication(s) [1]

Exondys 51® 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 51 skipping. This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with Exondys 51®.

Clinical Efficacy [1] (mechanism of action/pharmacology, comparative efficacy)

Exondys 51® is designed to bind to exon 51 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 51 skipping. Exon skipping is intended to allow for production of an internally truncated dystrophin protein.

Pharmacokinetics:

	Exondys 51®
Protein binding	6-17%
Excretion	Renal clearance accounts for approximately 2/3 of administered dose within 24 hours of IV administration
Half-life	3-4 hours
Volume of distribution	600 ml/kg following IV infusion at 30 mg/kg

Exondys 51® did not show a significant different in change in the 6 minute walk test compared to placebo. Dystrophin protein levels were not determined prior to the study, therefore it was not possible to estimate the dystrophin production in response to Exondys 51®.

Study 1

STUDY DESIGN	Randomized, double-blind, placebo-controlled, 24 week trial (n=12).
INCLUSION CRITERIA	Patients with confirmed mutation of the DMD gene and on a stable dose of corticosteroids for at least 6 months.
EXCLUSION CRITERIA	Not specified
TREATMENT REGIMEN	Patients were randomized to receive weekly infusions of Exondys 51® (30 mg/kg, n=4), Exondys 51® (50 mg/kg, n=4), or placebo (n=4) for 24 weeks.
RESULTS	The primary endpoint was dystrophin production. However, because of insufficient information on dystrophin protein levels before treatment, it is not possible to estimate dystrophin production in response to Exondys 51®. The 6 minute walk test was also assessed. This measures the distance that a patient can walk on a flat, hard surface in a period of 6 minutes. There was no significant difference between patients treated with Exondys 51® and those treated with placebo.
SAFETY	Not specified.

Study 2

STUDY DESIGN	All 12 patients who participated in Study 1 continued treatment with open-label Exondys 51® weekly for an additional 4 years. The 4 patients receiving placebo were rerandomized 1:1 to Exondys 51® 30 mg/kg or 50 mg/kg.
INCLUSION CRITERIA	Patients who participated in Study 1
EXCLUSION CRITERIA	Not specified
TREATMENT REGIMEN	Patients received either Exondys 51® 30 mg/kg/week (n=6) or Exondys 51® 50 mg/kg/week for an additional 4 years.
RESULTS	The primary efficacy measure was the 6 minute walk test. This was compared to an external control group. 11 patients had a muscle biopsy after 180 weeks of treatment, which was analyzed for dystrophin protein

	level by Western blot. Study 2 failed to provide evidence of a clinical benefit of Exondys 51® compared to the control group. The average dystrophin protein level after 180 weeks of treatment was 0.93% of the dystrophin level in healthy subjects.
SAFETY	Not specified.

Patients treated with Exondys 51® had a median increase of 0.1% in their dystrophin level.

Study 3

STUDY DESIGN	Open-label study (n=13)
INCLUSION CRITERIA	Patients with a confirmed mutation of the DMD gene and on a stable dose of corticosteroids for at least 6 months.
EXCLUSION CRITERIA	Not specified
TREATMENT REGIMEN	Patients received Exondys 51® 30 mg/kg weekly for 48 weeks and had a muscle biopsy at baseline and after 48 weeks of treatment.
RESULTS	In the 12 patients with evaluable results, the pre-treatment dystrophin level was 0.16% ± 0.12% of the dystrophin level in a healthy subject and 0.44% ± 0.43% after 48 weeks of treatment. The median increase after 48 weeks was 0.1%.
SAFETY	Not specified.

Contraindications (1)

- None

Warnings and Precautions (1)

- None listed in manufacturer labeling

Adverse Effects (1)

Most common, ≥ 25 % more than placebo	Exondys 51® (n=8)	Placebo (n=4)
Balance Disorder	38%	0%
Vomiting	38%	0%

Contact dermatitis	25%	0%

Drug Interactions [1]

- No knows interactions

Dosage and Administration [1]

The FDA recommended dose is 30 mg/kg administered once weekly as a 35 to 60 minute intravenous infusion.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	Dose	COST/ MONTH*
Eteplirsen	Exondys 51	Serepta	100 mg/ 2 ml vial	30 mg/kg	$808/ml
			500 mg/ 10 ml vial	30 mg/kg	$808/ml

*Maximum Allowable Cost

Conclusion

Exondys 51® is designed to bind to exon 51 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutation that are amenable to exon 51 skipping. Exon skipping is intended to allow for production of an internally truncated dystrophin protein. Exondys 51® is the first drug given approval for the treatment of Duchenne muscular dystrophy (DMD). This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with Exondys 51®. However, a clinical benefit has not yet been established.

Recommendation

The MO HealthNet Division recommends prior authorization status for this product.

References

1. Exondys 51. Retrieved 11/29/2016 from https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=33bff678-7829-479e-9110-b8e33a0bc0aa
2. FDA grants accelerate approval to first drug for Duchenne muscular dystrophy. Retrieved 11/29/2016 from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm521263.htm

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