Formulary Drug Reviews

Eteplirsen

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Each month, subscribers to *The Formulary Monograph Service* receive 5 to 6 well-documented monographs on drugs that are newly released or are in late phase 3 trials. The monographs are targeted to Pharmacy & Therapeutics Committees. Subscribers also receive monthly 1-page summary monographs on agents that are useful for agendas and pharmacy/nursing in-services. A comprehensive target drug utilization evaluation/medication use evaluation (DUE/MUE) is also provided each month. With a subscription, the monographs are available online to subscribers. Monographs can be customized to meet the needs of a facility. Through the cooperation of *The Formulary, Hospital Pharmacy* publishes selected reviews in this column. For more information about *The Formulary Monograph Service*, contact Wolters Kluwer customer service at 866-397-3433. The April 2017 monograph topics are deflazacort, plecanatide, delafloxacin, oxymetazoline hydrochloride 1% cream, and betrixaban. The DUE is on plecanatide.

Generic Name:	Eteplirsen
Proprietary Name:	Exondys 51 (Sarepta Therapeutics)
Approval Rating:	1 P
Therapeutic Class:	Antisense oligonucleotides
Similar Drugs:	None
Sound- or Look-Alike Names:	None

INDICATIONS

Eteplirsen is approved 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.^{1,2}

DMD is a genetic disease that affects 1 per 3,500 to 6,000 live male births and is the most common type of childhood muscular dystrophy. It is associated with a deficiency of dystrophin at the muscle sarcolemma, which causes destabilization of the muscle membrane and presents as a delay in motor development, calf hypertrophy, joint contractures, and progressive muscle weakness. Consequences of DMD include progressive muscle degeneration, loss of ambulation, scoliosis, cardiomyopathy, respiratory insufficiency, and reduced life expectancy. No cure for

DMD exists, and no drugs have been approved with documented clinical benefit. The current treatment strategies for DMD include supportive therapies (eg, family-centered care, social services), well-balanced diet, participation in physical and recreational activities, and pharmacologic and psychosocial support to delay the onset of secondary complications, including the use of corticosteroids and other anti-inflammatory drugs. Emerging treatment strategies include dystrophin gene replacement, use of exon-skipping compounds (eg, drisapersen, eteplirsen), nonsense suppression therapy (eg, ataluren), cell therapy using muscle precursor cells or stem cells, membrane stabilization and upregulation of cytoskeletal proteins, regulation of intracellular calcium and mitochondria, counteraction of oxidative stress, and the development of noncorticosteroid or anti-inflammatory agents that do not inhibit prostaglandin synthesis.^{3–6}

CLINICAL PHARMACOLOGY

Eteplirsen is a synthetic antisense oligonucleotide from the phosphorodiamidate morpholino oligomer subclass of molecules. In these types of molecules, 5-membered ribofuranosyl rings found in natural DNA and RNA are replaced by a 6-membered morpholino ring. Eteplirsen binds to exon 51 of dystrophin

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pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 51 skipping. By skipping exon 51, the body produces an internally truncated dystrophin protein.^{1,3,7-9} Dystrophin connects with other proteins to form the dystrophin-associated glycoprotein complex. The absence of dystrophin and subsequent destabilization of the dystrophin-associated glycoprotein complex results in muscle cells that are susceptible to stretch-induced damage and increased intracellular calcium influx. This is followed by a series of pathological processes that lead to skeletal and cardiac muscle fiber necrosis, inflammation, replacement of muscle with fibro-adipose tissue, and altered blood flow in skeletal muscle.^{9,10} Elevated serum levels of this truncated dystrophin protein were used as the surrogate marker in DMD studies, but the long-term impact on motor functions and disease progression remains unknown.¹¹

PHARMACOKINETICS

Following single or multiple intravenous (IV) infusions of eteplirsen, peak serum levels (C_{max}) occurred near the end of infusion (ie, 1.1 to 1.2 hours across a dose range of 0.5 mg/kg/week to 50 mg/kg/week).¹

In dose-ranging studies, changes in pharmacokinetic parameters followed a linear and dose-proportional model. The majority of drug elimination occurred within 24 hours of administration. The intersubject variability for C_{max} and area under the curve (AUC) ranged from 20% to 55%.^{1,8,12}

Plasma protein binding was low (6% to 17%).¹ The mean apparent volume of distribution was 600 mL/kg.^{1,8} The total clearance of eteplirsen was 339 mL/h/kg following 12 weeks of therapy at the recommended dose (30 mg/kg/week).¹ Renal clearance accounted for about two-thirds of the administered dose. The elimination half-life of eteplirsen was 3 to 4 hours.^{1,8,12,13} The impact of age, gender, race, or renal or hepatic impairment on the pharmacokinetics of eteplirsen has not been evaluated.¹

COMPARATIVE EFFICACY

Indication: Duchenne Muscular Dystrophy

Studies

Drug: Eteplirsen vs Placebo

Reference: Mendell JR, et al, 2013; Mendell JR, et al, 2016 (Studies 201 and 202)^{13,14}

Study Design: Randomized, double-blind, placebo-controlled, multicenter study followed by an open-label extension study

Study Funding: Sarepta Therapeutics

Patients: 12 boys 7 to 13 years of age with confirmed out-of-frame DMD deletions potentially correctable by skipping exon 51 and with an ability to walk 200 to 400 m on the 6-minute walk test (6MWT). Patients had to be on a stable dose of glucocorticoids for at least 24 weeks prior to enrollment. The mean 6MWT distance at baseline was 381.9 m, but the mean distance walked by the group assigned to treatment with eteplirsen 30 mg/kg/week was about 40 m less than the other 2 groups.

Intervention: Patients were randomly assigned to treatment with eteplirsen 30 mg/kg, eteplirsen 50 mg/kg, or placebo for 24 weeks in the double-blind, placebo-controlled, phase 2b portion (Study 201). Patients randomized to placebo were then switched at week 25 to either eteplirsen 30 mg/kg/week or eteplirsen 50 mg/kg/week for the 24-week open-label extension portion of the study (Study 202). Patients previously randomized to eteplirsen 30 mg/kg or eteplirsen 50 mg/kg continued their original dosing. Eteplirsen was diluted in normal saline and the placebo group received phosphate-buffered saline. Both solutions were given by IV infusion over 60 minutes at weekly intervals.

Results

Primary Endpoint(s)

- Dystrophin production at week 12 was not different from placebo.¹³

Secondary Endpoint(s)

- Dystrophin-positive fibers were detected at week 24 and were significantly different for the 30 mg/kg and 50 mg/kg groups compared with placebo at week 48 (47.3%; $p \leq .001$).¹³
- Mean fluorescence signal intensity of muscle fibers expressing MANDYS106 at week 48 was greater with both doses of eteplirsen compared to placebo.¹³
- Adjusted mean change in the 6MWT distance at week 24 was -25.8 m with placebo, -128.2 m with eteplirsen 30 mg/kg, and -0.3 m for eteplirsen 50 mg/kg. The decline in the eteplirsen 30 mg/kg group was related to 2 patients with rapid disease progression. When these 2 patients were excluded, the adjusted mean change from baseline was 14.2 m. Analysis of covariance (ANCOVA) for ranked data showed no significant difference among the 3 groups. The adjusted mean change in 6MWT distance at week 48 was -68.4 m for placebo,

-153.4 m for eteplirsen 30 mg/kg, and 21.0 m for eteplirsen 50 mg/kg. The decline in the eteplirsen 30 mg/kg group was a result of the same 2 patients previously described, and the adjusted mean change from baseline was 31.5 m when the 2 patients were excluded. ANCOVA for ranked data showed no significant difference between placebo and eteplirsen 30 mg/kg, but it did reach significance between the eteplirsen 50 mg/kg and placebo/delayed cohorts ($p \leq .016$).¹³

- Pulmonary function tests remained relatively stable during the 36-month study.¹⁴

Comments: Use of a mixed model repeated measurement was intended to evaluate the change from baseline in 6MWT data; however, due to strong evidence of deviation from normality, ANCOVA for ranked data was used. The prescribing information also includes data from an open-label study (Study 301) in which 13 patients were treated with eteplirsen 30 mg/kg weekly for 48 weeks. The pretreatment dystrophin level was 0.16% of the dystrophin level in a healthy subject and 0.44% after 48 weeks of eteplirsen treatment; treatment difference from baseline to week 48 was 0.28% ($p = .008$).

Limitations: The study population was very small, with only 4 patients in each group. Two patients assigned to eteplirsen experienced rapid disease progression during the study. The number of patients in the historical control group who matched the inclusion criteria was also small ($n = 13$). The open-label portion of the study had no control group, so the authors did a case-control evaluation against matched, untreated, historical controls from the Leuven Neuromuscular Reference Center and the Italian Telethon registry. At 36 months, eteplirsen-treated patients demonstrated a statistically significant advantage of 151 m on 6MWT and experienced a lower incidence of loss of ambulation compared to the matched historical control group (16.7% vs 46.2%).¹⁴

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

None.¹

Warnings and Precautions

None.¹

No data exist regarding the safety of eteplirsen use during pregnancy or breast-feeding.¹

No data exist regarding the safety or effectiveness of eteplirsen in patients with renal or hepatic impairment.¹

ADVERSE REACTIONS

In Study 201 (8 patients treated with eteplirsen, 4 with placebo), the most common adverse reactions with eteplirsen were balance disorder (38% vs 0% with placebo), vomiting (38% vs 0% with placebo), and contact dermatitis (25% vs 0% with placebo).^{1,14} Adverse reactions reported on the day of infusion were transient erythema, facial flushing, and elevated temperature. Other adverse reactions reported with eteplirsen were contusion, excoriation, arthralgia, rash, catheter-site pain, and upper respiratory tract infection.^{1,14}

DRUG INTERACTIONS

No drug-drug interactions are anticipated. In vitro data showed that eteplirsen does not significantly inhibit cytochrome P450 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5 or induce CYP2B6 or 3A4. Eteplirsen does not appear to be metabolized by hepatic microsomes. Eteplirsen is not a substrate of and does not have major inhibitory potential for key human transporters (eg, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, P-gp, BCRP, MRP2, BSEP).^{1,15}

RECOMMENDED MONITORING

No special monitoring is recommended.

DOSING

The recommended dose of eteplirsen is 30 mg/kg of body weight once weekly as an IV infusion over 35 to 60 minutes.¹ Some patients may require the use of a topical anesthetic cream applied to the infusion site prior to eteplirsen administration.¹

Eteplirsen comes as a concentrated solution and must be diluted with 0.9% sodium chloride injection, USP prior to IV administration.¹

The intravenous access line should be flushed with 0.9% sodium chloride injection, USP prior to and after infusion.¹ Do not mix eteplirsen with other medications or infuse other medications concomitantly via the same IV access line.¹

PRODUCT AVAILABILITY

Eteplirsen was approved under the accelerated approval provisions of the FDA process in September 2016, based on initial data predicting clinical benefit (ie, increased dystrophin production in skeletal muscle observed in some patients treated with eteplirsen).

However, the FDA requires that Sarepta Therapeutics conduct a clinical trial to confirm the drug's clinical benefit (eg, improved motor function).^{2,16} Eteplirsen was also granted priority review and orphan drug designation.¹⁶

Eteplirsen is available in a single-dose vial as a preservative-free concentrated solution of 100 mg per 2 mL or 500 mg per 10 mL.¹ The drug should be protected from light and freezing and stored in the original carton until ready for use.¹

The diluted solution should be administered immediately after dilution and the infusion completed within 4 hours. The diluted solution can be stored for up to 24 hours at 2°C to 8°C (36°F to 46°F).¹

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

No REMS is required for eteplirsen.²

CONCLUSION

Eteplirsen is an orphan drug approved for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. It was approved under the accelerated approval process based on increased levels of the deficient protein (ie, dystrophin) in skeletal muscle. As a condition of continued FDA approval, Sarepta Therapeutics will need to complete a clinical study to confirm the drug's clinical benefit (eg, improved motor function) in the treatment of DMD.

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