Exondys 51 (eteplirsen)

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This Medical Policy document describes the status of medical technology at the time the document was developed. Since that time, new technology may have emerged or new medical literature may have been published. This Medical Policy will be reviewed regularly and be updated as scientific and medical literature becomes available.

DESCRIPTION

Exondys 51 (eteplirsen) is indicated for treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. It is administered once weekly as an intravenous (IV) infusion and may be used as monotherapy or in combination with corticosteroids.

This indication was approved by the Food and Drug Administration (FDA) in September 2016 under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with Exondys 51. A clinical benefit of Exondys 51 has not been established.

POLICY

Exondys 51 (eteplirsen) is considered **not medically necessary** for all indications, including the treatment for DMD, due to insufficient evidence to demonstrate clinical efficacy.

CLINICAL RATIONALE

Exondys 51 (eteplirsen) is an exon-skipping therapy that targets dystrophin pre-messenger ribonucleic acid (mRNA) and induces skipping of mutated exons of the DMD gene that disrupt downstream protein synthesis

and lead to nonfunctional or absent dystrophin. Skipping mutated exons results in restoration of small amount of dystrophin.

Clinical Studies

FDA approval of Exondys 51 (eteplirsen) was based on three clinical studies in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. The trials were not designed to evaluate long-term safety, and a clinical benefit of Exondys 51 (eteplirsen) has not been established.

In Study 1, a double-blind, placebo-controlled study, patients were randomized to receive weekly infusions of eteplirsen (30 mg/kg, n=4); eteplirsen (50 mg/kg, n=4), or placebo (n=4) for 24 weeks. The primary endpoint was dystrophin production; a clinical outcome measure, the 6-minute walk test (6MWT), was also assessed. The 6MWT measures the distance that a patient can walk on a flat, hard surface in a period of 6 minutes. Patients had a mean age of 9.4 years, a mean 6-minute walk distance (6MWD) at baseline of 363 meters, and were on a stable dose of corticosteroids for at least 6 months. There was no significant difference in change in 6MWD between patients treated with eteplirsen and those treated with placebo.

All 12 patients who participated in Study 1 continued treatment with open-label eteplirsen weekly for an additional 4 years in Study 2. The 4 patients who had been randomized to placebo were re-randomized 1:1 to eteplirsen 30 or 50 mg/kg/week such that there were 6 patients on each dose. Patients who participated in Study 2 were compared to an external control group. The primary clinical efficacy outcome measure was the 6MWT. Eleven patients in Study 2 had a muscle biopsy after 180 weeks of treatment with eteplirsen, which was analyzed for dystrophin protein level by Western blot. Study 2 failed to provide evidence of a clinical benefit of eteplirsen compared to the external control group. The average dystrophin protein level after 180 weeks of treatment with eteplirsen was 0.93% of the dystrophin level in healthy subjects. Because of insufficient information on dystrophin protein levels before treatment with eteplirsen in Study 1, it is not possible to estimate dystrophin production in response to eteplirsen in Study 1.

In Study 3, 13 patients were treated with open-label eteplirsen (30 mg/kg) weekly for 48 weeks and had a muscle biopsy at baseline and after 48 weeks of treatment. Patients had a mean age of 8.9 years and were on a stable dose of corticosteroids for at least 6 months. Dystrophin levels in muscle tissue were assessed by Western blot. In the 12 patients with evaluable results, the pre-treatment dystrophin level was 0.16% ± 0.12% (mean ± standard deviation) of the dystrophin level in a healthy subject and 0.44% ± 0.43% after 48 weeks of treatment with eteplirsen ($p < 0.05$). The median increase after 48 weeks was 0.1% in the dystrophin levels after treatment with eteplirsen. A statistically significant, yet marginal, increase in dystrophin was reported (0.22% to 0.32% of normal) but there was no evidence proving that this increase translated to a clinical benefit.

Study 204 (NCT02286947) is an unpublished open-label, multicenter study, designed to evaluate the safety and tolerability of eteplirsen treatment in non-ambulatory males aged 7 to 21 years with a diagnosis of DMD and DMD gene mutation(s) amenable to exon 51 skipping. All patients were taking a stable dose of oral glucocorticoids or had not received glucocorticoids for at least 24 weeks prior to study drug administration, were minimally ambulatory or non-ambulatory (defined as taking longer than 30 seconds to independently walk 10 meters or being incapable of walking ≥300 meters on the 6MWT), and had stable cardiac and respiratory function. All patients received once-weekly intravenous infusions of 30 mg/kg of eteplirsen for 96 weeks, followed by a safety extension period up to 48 weeks. Respiratory function tests (including FVC%p) were assessed every 12 weeks for the first year of the study, and every 24 weeks thereafter through 96 weeks, for a total duration of 2 years. Study results for the safety outcomes measured can be found on clinicaltrials.gov. The most common adverse events reported were nasopharyngitis (58.3%), back pain (37.5%), headache (33.3%), vomiting (29.2%), cough (29.2%), abdominal pain (25%), and upper respiratory tract infection (25%).

Study 301 (PROMOVI, NCT02255552) was a multicenter, open-label, Phase III study of male patients aged 7 years to 16 years with a diagnosis of DMD that is amenable to exon 51 skipping. Eligible patients were ambulatory with a 6MWT of 300 meters or more, on a stable dose of oral glucocorticoids prior to entering the trial, and had stable respiratory function. All patients received a once-weekly intravenous infusion of 30 mg/kg of eteplirsen for 96 weeks later followed by a safety extension. The primary endpoint was the change from baseline in the 6MWT at 96 weeks with a secondary endpoint that evaluated the change in the percentage of dystrophin positive fibers. Change in pulmonary function was an exploratory endpoint. The interim analysis published by Khan et al (2019) showed a decline of 3.79% annually in the FVC%p. Final results included a post hoc analysis of 6MWT which reported a mean change from baseline of -68.9 meters (n = 42) compared with -133.8 meters in external natural history controls (n = 11). The annual rate of decline in FVC%p was -3.3% (n = 52) in POMOVI while the matched historical cohort experienced a -6.0% decline (n = 20). A significant increase was demonstrated in exon 51 skipping muscle fibers and dystrophin protein expression.

An additional study conducted to assess eteplirsen's safety, tolerability, pharmacokinetics, and efficacy in male patients ages 6 months to 48 months who have genotypically confirmed DMD with a deletion amenable to exon 51 skipping (NCT03218995) concluded the safety profile was consistent with the known safety profile of eteplirsen, was well tolerated with no evidence of kidney toxicity, and the pharmacokinetics were comparable to that of boys older than 4 years old.

Lastly, an assessment of the long-term safety and tolerability of eteplirsen in patients who had already received 96 weeks of treatment with eteplirsen (NCT03985878) was terminated as in August 2023. A remaining ongoing trial includes a comparison between two high doses, 100 mg/kg and 200 mg/kg, of eteplirsen (NCT03992430, MIS51ON). MIS51ON is a two-part study, where the second part will compare the safety and efficacy of a single, selected high dose of eteplirsen to the 30 mg/kg dose. Estimated study completion is October 2026.

Additional Data Analyses

Randeree et al (2018) conducted a pooled analysis of studies evaluating the use of eteplirsen for the treatment of patients with DMD. A literature search, conducted through November 2017, identified 3 studies (N=38 patients) for inclusion in the analyses. The 3 studies consisted of a non-randomized dose escalation study, an open-label dose-escalation study, and a study described above. A quality assessment of the studies was not performed. The average increase in percent dystrophin-positive fibers was 24.2% (standard deviation, 24.4%) and the average rate of decline in 6MWT was 65 m (standard deviation=100.1). The clinical significance of these results is unclear and the authors concluded that further evidence is required.

Kinane et al (2018) conducted a case-control study of long-term pulmonary function in patients with DMD treated with eteplirsen compared with historical controls. Cases were 1) patients from the original trial cohort of 12 patients between 7 years and 13 years with confirmed deletions amenable to skipping exon 51 and ability to walk 200-400 m on 6MWT and on glucocorticoids for ≥24 weeks; and 2) historical controls were patients between 7 years and 15.5 years in the United Dystrophinopathy Project (UDP) who had undergone pulmonary function testing. All patients in the UDP had confirmed dystrophin variant. The annual decline in FVC was not significantly different between groups. The annual decrease in FVC in the historical controls was 4.1% (95% confidence interval, 1.9% to 6.3%) and the annual decrease in FVC in the cases treated with eteplirsen was 2.3% (95% confidence interval, 1.2% to 3.4%).

Khan et al (2019) evaluated respiratory function in eteplirsen-treated patients from three of four open-label clinical trials, (studies 1, 2, 204, and 301 mentioned above) which included ambulatory DMD patients and non-ambulatory DMD patients. Respiratory function of the eteplirsen-treated patients was compared to that of patients using only glucocorticoids using the Cooperative International Neuromuscular Research Group Duchenne Natural History Study (CINRG DNHS) global database. Results showed that all the eteplirsen-

treated patients had a significantly slower decline in respiratory function compared to matched controls in the CINRG DNHS group with a mean annual decline of 2-4% compared to 6%. Patients in two of the studies (Studies 201/202) received 4 years of eteplirsen treatment and the annual decline in FVC%p was reduced to 2.19%. In contrast, in the 2-year study 204 and the interim analysis of 2-year study 301, annual declines of 3.66% and 3.79%, respectively, were observed. The slower rate of respiratory decline is clinically meaningful but it is still unknown if that would translate to prolonged time to required mechanical airway clearance, noninvasive ventilation, reduced risk of hospitalization due to respiratory illnesses, improved quality of life, and improved survival. The study findings also suggest that the longer duration of eteplirsen treatment may result in progressive attenuation of muscle function decline. The authors noted that a further analysis of the duration of eteplirsen treatment is warranted.

In summary, the clinical benefit of treatment for DMD with Exondys 51 (eteplirsen) has not been demonstrated. The establishment of a clinical benefit, including improved motor function and pulmonary function, is warranted in on-going clinical trials. The following conclusion is also stated in the FDA prescribing information, “A clinical benefit of Exondys 51 (eteplirsen) has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.”.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- J1428 Injection, eteplirsen, 10mg, Exondys 51

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pharmacokinetics of eteplirsen in young boys aged 6–48 months with Duchenne muscular dystrophy amenable to exon 51 skipping, Neuromuscular Disorders, Volume 33, Issue 6, 2023, Pages 476-483

POLICY HISTORY

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