SPECIALTY GUIDELINE MANAGEMENT
Eteplirsen (Exondys 51™)

Background:
Eteplirsen (Exondys 51™) is a new antisense oligonucleotide indicated for the treatment of Duchenne muscular dystrophy (DMD), a recessive X-linked myopathy in which a person is unable to properly synthesize dystrophin, a protein essential to the maintenance of muscle cell membrane integrity, and thus suffers progressive muscle deterioration. Eteplirsen is designed to facilitate functional dystrophin production by causing gene expression to skip exon 51 on the *DMD* gene, the exon associated with approximately 13% of DMD-causing mutations.

Authorization:
Prior authorization is required for eteplirsen (Exondys 51™) requested by members enrolled in commercial (HMO, POS and PPO) products.

Policy and Coverage Criteria:

Initiation of Therapy:
Harvard Pilgrim Health Care (HPHC) considers initiation of injected eteplirsen (Exondys 51™) as reasonable and medically necessary for the management of Duchenne muscular dystrophy (DMD) for a maximum of six months when medical record documentation confirm ALL of the following;

A. Member DMD is due to mutation of the *DMD* gene amenable to exon 51 skipping and no other DMD-associated mutations;
B. Ongoing use of a stable dose of corticosteroids going back at least six months or a contraindication to corticosteroids;
C. Member is able to average a 180 meter 6-minute walk test (6MWT);
D. Assessment and prescription were performed by a physician specializing in DMD;
E. Dosage and use is consistent with FDA labelling (30mg per kilogram of body weight per week)

Continuation of Therapy:
Harvard Pilgrim Health Care (HPHC) considers a continuation of injected eteplirsen (Exondys 51™) for a maximum of six months as reasonable and medically necessary for the management of Duchenne muscular dystrophy (DMD) upon verification of a clinical benefit, when medical record documentation confirm ALL of the following;

A. Member met the above initiation conditions at start of treatment;
B. Member shows response to treatment evidenced by continued independent ambulation;
C. Dosage and use is consistent with FDA labelling (30mg per kilogram of body weight per week)

Exclusions:
Harvard Pilgrim Health Care (HPHC) does not cover eteplirsen (Exondys 51™) injections when criteria above are not met.

Supporting Information:
There are four main extant trials assessing eteplirsen as an injection, NCT00844597, NCT01396239, NCT01540409, and NCT02255552. The study NCT00844597, a non-controlled twelve-week trial meant primarily to assess safety and tolerability, found improvements in dystrophin expression in seven of nineteen patients, with three patients showing especially clinically significant improvements. Additionally, there was variation in measurements between readings. The inconsistency of effect was ascribed to a mix of differences in the amenability of underlying mutations to being suppressed by eteplirsen and the short duration of the trial. Two follow-up trials, NCT01396239 and NCT01540409 were extended responses to the previous trial focusing primarily on efficacy, with the former being a twenty-four-week randomized control trial and the latter being a four-year extension of the former in which the controls were also placed on eteplirsen. Patients on eteplirsen were

stratified into two dosage levels (30mg/kg-body weight per week and 50mg/kg-body weight per week). Both dosage levels showed improvement in dystrophin levels against both initial condition and control group. The higher dosage group showed improved six-minute-walk tests compared to the delayed treatment group at forty-eight weeks. In long term progress, participants showed declines in ambulation and vital function capacities that were considerably delayed compared to established benchmarks, but declines all the same.
Adverse events attributed to eteplirsen in long term study included vomiting, headaches, balance disorders, and proteinuria. Other adverse events, such as cardiac fractional shortening, were observed but were typical of patients suffering from DMD and not observed at an unusual rate for the sample population.
Eteplirsen received FDA approval in September of 2016, for weekly dosages of 30mg per kilogram of body weight, for the treatment of DMD in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 51 skipping. Eteplirsen received an accelerated approval due to DMD holding orphan disease status, however the FDA labelling states continued approval may be contingent upon verification of a clinical benefit in confirmatory trials.

Coding:

CPT® Code	**Description**
J1428	Injection, eteplirsen (Exondys 51®), 10 mg

ICD10® Code	**Description**
G71.0	Muscular Dystrophy (Duchenne muscular dystrophy [DMD])

References:

1. Hathout Y, Seol H, Han MHJ, Zhang A, Brown KJ, Hoffman EP. Clinical utility of serum biomarkers in Duchenne muscular dystrophy. *Clinical Proteomics*. 2016;13(1). doi:10.1186/s12014-016-9109-x.
2. Arechavala-Gomeza V, Graham IR, Popplewell LJ, et al. Comparative Analysis of Antisense Oligonucleotide Sequences for Targeted Skipping of Exon 51 During Dystrophin Pre-mRNA Splicing in Human Muscle. Human Gene Therapy. 2007;18(9):798-810. doi:10.1089/hum.2006.061.
3. Mendell JR, Rodino-Klapac LR, Sahenk Z, et al. Eteplirsen for the treatment of Duchenne muscular dystrophy: Eteplirsen for DMD. Annals of Neurology. 2013;74(5):637-647. doi:10.1002/ana.23982.
4. Lim KR, Maruyama R, Yokota T. Eteplirsen in the treatment of Duchenne muscular dystrophy. Drug Design, Development and Therapy. 2017;Volume11:533-545. doi:10.2147/DDDT.S97635.
5. Cirak S, Arechavala-Gomeza V, Guglieri M, et al. Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study. The Lancet. 2011;378(9791):595-605. doi:10.1016/S0140-6736(11)60756-3.
6. Kole R, Krieg AM. Exon skipping therapy for Duchenne muscular dystrophy. Advanced Drug Delivery Reviews. 2015;87:104-107. doi:10.1016/j.addr.2015.05.008.
7. Mendell JR, Goemans N, Lowes LP, et al. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy: Eteplirsen in DMD. Annals of Neurology. 2016;79(2):257-271. doi:10.1002/ana.24555.
8. Henricson E, Abresch R, Han JJ, et al. Percent-Predicted 6-Minute Walk Distance in Duchenne Muscular Dystrophy to Account for Maturational Influences. PLoS Currents. 2012;4:RRN1297. doi:10.1371/currents.RRN1297.
9. Ricotti V, Ridout DA, Pane M, et al. The NorthStar Ambulatory Assessment in Duchenne muscular dystrophy: considerations for the design of clinical trials. Journal of Neurology, Neurosurgery & Psychiatry. March 2015:jnnp-2014-309405. doi:10.1136/jnnp-2014-309405.
10. Ricotti V, Evans MRB, Sinclair CDJ, et al. Upper Limb Evaluation in Duchenne Muscular Dystrophy: Fat-Water Quantification by MRI, Muscle Force and Function Define Endpoints for Clinical Trials. Musaro A, ed. *PLOS ONE*. 2016;11(9):e0162542. doi:10.1371/journal.pone.0162542.