New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Viltepso® (viltolarsen) [NS Pharma]**
Dosage Formulations:	250 mg/5 mL solution for injection available as a single-dose vial
FDA Approval Date: **FDB File Date:**	FDA: August 12, 2020 FDB: August 23, 2020
Indication:	Treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping
Mechanism of Action:	Binds 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. Exon 53 skipping is intended to allow for production of an internally truncated dystrophin protein in patients with genetic mutations that are amenable to exon 53 skipping.
Dose/ Administration:	80 mg/kg administered once weekly as a 60-minute intravenous (IV) infusion
Drug Clinical Highlights:	• Received Priority Review, Rare Pediatric Disease, Orphan Drug, and Fast Track designations. • Received accelerated approval based on an increase in dystrophin production in skeletal muscles. • Efficacy was based on a Phase II, multicenter, 2-period, randomized, placebo-controlled, dose-finding study (n=16) that included ambulant males aged 4 to less than 10 on a stable corticosteroid regimen for at least 3 months. Period 1, the initial period, consisted of 4 weeks during which patients were randomized to receive IV Viltepso 40 mg/kg or placebo. During Period 2, all patients received active treatment with either 40 mg/kg or 80 mg/kg Viltepso once weekly for 20 weeks. • Muscle biopsies were collected at baseline and 24 weeks to determine the change in baseline dystrophin protein level in order to assess Viltepso efficacy. • Primary Endpoint: Dystrophin protein in muscle as measured by western blot (time frame: 20-24 weeks of treatment) ○ In the 8 patients that received Viltepso 80 mg/kg once weekly, mean dystrophin levels increased from 0.6% of normal at baseline to 5.9% of normal by week 25, with a mean change in dystrophin of 5.3% of normal levels. Median change from baseline was 3.8%. • Contraindications: none • Warnings/Precautions: kidney toxicity was observed in animal studies but was not confirmed in clinical trials. Due to reports of potentially fatal glomerulonephritis in other antisense oligonucleotides, renal function monitoring is recommended. • Adverse reactions: upper respiratory tract infection, injection site reactions, cough, pyrexia, contusion, arthralgia, diarrhea, vomiting, abdominal pain, decreased ejection fraction, urticaria • Similar to other agents indicated for DMD, Viltepso's safety and efficacy in females is unknown.

Disease State Clinical Highlights:	• DMD is a fatal X-linked genetic disorder resulting from absent or defective dystrophin protein. Dystrophin levels of affected patients are usually less than 3% of normal; dystrophin is needed for normal muscle maintenance and function. DMD results in progressive and irreversible loss of muscle function.
	• The amount of dystrophin needed for functional improvement is currently unknown.
	  ○ Results from a study on *mdx* mice revealed the level needed for normal neuromuscular function is between 19 – 50%.
	  ○ Another study on *mdx* mice revealed that levels of dystrophin needed to improve muscle function were as low as 5 – 15%.
	  ○ An analysis of female carriers of DMD revealed that asymptomatic carriers had 50 – 65% of normal dystrophin protein, while those with less than 50% of normal display clear symptoms of muscle weakness.

- DMD almost exclusively affects males. Females can be carriers; it is extremely rare for a female to inherit two affected X chromosomes.
- 20,000 males in the United States have DMD. 1 in 3,000 – 5,000 newborn boys are affected.
- Approximately 80% of DMD patients have skippable mutations; most are concentrated between exons 45 and 53.
  - 13% have exon 51 mutations
  - 8% have exon 53 mutations
  - 8% have exon 45 mutations
  - 6% have exon 44 mutations
- Most DMD patients require the use of a wheelchair by age 12, respiratory support by age 20, and death resultant to cardiac or respiratory failure often occurs by age 30.
- Standard of care for DMD has historically been management of symptoms.
  - Use of glucocorticoids for neuromuscular symptoms.
  - Physical and occupational therapy
  - Surgery to improve gait in select patients
  - Standard heart failure treatment for deterioration of cardiac function
  - Initiation of ACE/ARB by age 10 years
  - Bisphosphonates for bone fragility
  - Gastrostomy placement for severe dysphagia
  - Lung volume recruitment therapy for FVC <60%
  - Ventilation / cough assistance for hypoxemia

Price Per Unit (WAC):

$1,410 per vial
$733,200 annually for a 30 kg patient (requires 10 vials per dose)

Therapeutic Alternatives:

Viltepso represents the third antisense oligonucleotide approved for DMD following Exondys 51 and Vyondys 53. Viltepso will likely directly compete with Vyondys 53 as both are indicated in patients with a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. Emflaza, a corticosteroid, is also indicated for DMD.

	Vyondys 53 (golodirsen)	Viltepso (viltolarsen)
Approval Date	December 2019	August 2020
Class	Antisense oligonucleotide	Antisense oligonucleotide
Dosage Form(s)	Solution for injection	Solution for injection
Dose	30 mg/kg weekly IV infusion	80 mg/kg weekly IV infusion
FDA Approved Age	Not specified	Not specified
Clinical Studies		
Trial Ages	≥ 6 to ≤ 15 years	≥ 4 to ≤ 10 years
Treatment Duration	52 Weeks	24 Weeks
Primary Endpoint	• Efficacy was assessed based on change from baseline in dystrophin protein level at Week 48 • Mean dystrophin levels increased from 0.1% (SD 0.07) of normal at baseline to 1.02% (SD 1.03) of normal by Week 48 • Mean change in dystrophin of 0.92% (SD 1.01) of normal levels (P < 0.001) • Median change from baseline was 0.88%	• Efficacy was assessed based on change from baseline in dystrophin protein level at Week 25 • Mean dystrophin levels increased from 0.6% (SD 0.8) of normal at baseline to 5.9% (SD 4.5) of normal by Week 25 • Mean change in dystrophin of 5.3% (SD 4.5) of normal levels (P = 0.01) • Median change from baseline was 3.8%
Common Adverse Reactions	Headache, pyrexia, fall, abdominal pain, nasopharyngitis, cough, vomiting, nausea	URI, injection site reaction, cough, pyrexia, contusion, arthralgia, diarrhea, vomiting, abdominal pain, decreased ejection fraction, urticaria
Annual WAC Price (30 kg patient)	$748,000	$733,200

URI: upper respiratory infection

Prior Authorization Approval Criteria:	**Must meet the following criteria:**
	
	Initial Therapy:
	• Documented diagnosis of DMD confirmed by:
	  ○ Genetic testing for dystrophin gene deletion or duplication **OR**
	  ○ Genetic sequencing screening for pathogenic variant attributed to DMD **OR**
	  ○ Positive muscle biopsy showing absence of dystrophin protein **AND**
	• Genetic testing to confirm pathogenic variant of DMD gene amenable to exon 53 skipping **AND**
	• Prescribed by or in consultation with a neurologist or other appropriate specialist **AND**
	• Age ≥ 4 to ≤ 10 years based on clinical study inclusion criteria **AND**
	• Documentation of baseline clinical criteria [ex: BMI, weight, ambulatory status, 6-minute walk test (6MWT), North Star Ambulatory Assessment (NSAA), Brooke Upper Extremity Function Scale, Forced vital capacity (FVC)] **AND**
	• Dosed at 80 mg/kg once weekly **AND**
	• Documentation of concurrent prednisone or deflazacort therapy, defined as 6 months in the past 9 months **AND**
	• Monitoring of serum cystatin C, urine dipstick and urine protein-to-creatinine ratio
	• Initial approval: 6 months
	
	Continuation of Therapy:
	• Improvement or stabilization of motor or pulmonary function from baseline (ex: 6MWT, NSAA, Brooke Upper Extremity Scare, FVC) **AND**
	• Participant retains meaningful voluntary motor function (ex: able to speak, manipulate objects using upper extremities, ambulate) **AND**
	• Renal function monitoring (urine dipstick monthly, serum cystatin C and urine protein-to-creatinine ratio every three months)
	• Reauthorization: 6 months

Implication to State Medicaid Program:	LOE Date: TBD **Pipeline** Pending Approval • Amondys 45 (casimersen) [Sarepta Therapeutics]: IV antisense oligonucleotide anticipated February 2021 Phase III Trials • Translarna (ataluren) [PTC Therapeutics]: oral inhibitor of premature protein translation termination • ITF2357 (givinostat) [Italfarmaco]: oral histone deacetylase (HDAC) inhibitor • FG-3019 (pamrevlumab) [FibroGen]: IV anti-CTGF antibody • BMS-986089 (TBD) [Bristol-Myers Squibb]: subcutaneous myostatin inhibitor • Edasa (edasalonexent) [Catabasis]: oral NF-kB inhibitor • PF-06939926 (TBD) [Pfizer]: IV gene therapy • Raxone (idebenone) [Santhera]: oral synthetic short-chain benzoquinone

References:

1. VILTEPSO (viltolarsen) [package insert]. Paramus, NJ: NS Pharma, Inc.; August 2020.
2. NIH: U.S. National Library of Medicine. “Safety and Dose Finding Study of NS-065/NCNP-01 in Boys with Duchenne Muscular Dystrophy (DMD). https://clinicaltrials.gov/ct2/show/NCT02740972?term=NCT02740972&draw=2&rank=1. Accessed 25 August 2020.
3. Birnkrant DJ, Bushby Katharine, et. al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. Lancet Neural. 23 January 2020. Accessed 25 August 2020; 17:251-67.
4. National Organization for Rare Disorders. “Duchenne Muscular Dystrophy.” https://rarediseases.org/rare-diseases/duchenne-muscular-dystrophy/#:~:text=The%20prevalence%20is%20estimated%20to,individuals%20in%20the%20United%20States.. Accessed 25 August 2020.
5. IPD Analytics Rx Insights_New Drug Review: Viltepso. Accessed 25 August 2020.
6. VYONDYS 53 (golodirsen) [package insert]. Cambridge, MA: Sarepta Therapeutics, Inc.; August 2020.