RXADVANCE
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NEW DRUG APPROVAL

Brand Name	VILTEPSO™
Generic Name	Viltolarsen
Drug Manufacturer	NS Pharma, Inc.

New Drug Approval

FDA Approval Date: August 12, 2020

Review Designation: Priority Review, Orphan

Review Type: Type 1 - NDA 212154

Dispensing Restrictions: None

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Duchenne muscular dystrophy (DMD) is a rare muscle disorder but it is one of the most frequent genetic conditions affecting approximately 1 in 3,500 male births worldwide. It is usually recognized between three and six years of age. DMD is characterized by weakness and wasting (atrophy) of the muscles of the pelvic area followed by the involvement of the shoulder muscles. As the disease progresses, muscle weakness and atrophy spread to affect the trunk and forearms and gradually progress to involve additional muscles of the body. In addition, the calves appear enlarged in most patients. The disease is progressive and most affected individuals require a wheelchair by the teenage years. Serious life-threatening complications may ultimately develop including disease of the heart muscle (cardiomyopathy) and breathing (respiratory) difficulties.

DMD is inherited as an X-linked disease. X-linked genetic disorders are conditions caused by an abnormal gene on the X chromosome and manifest mostly in males. Females that have a defective gene present on one of their X chromosomes are carriers for that disorder. Carrier females usually do not display symptoms because females have two X chromosomes and only one carries the defective gene. Males have one X chromosome that is inherited from their mother and if a male inherits an X chromosome that contains a defective gene he will develop the disease.

The muscular dystrophies as a whole are estimated to affect 250,000 individuals in the United States.

Efficacy

The effect of VILTEPSO™ on dystrophin production was evaluated in one study in DMD patients with a confirmed mutation of the DMD gene that is amenable to exon 53 skipping (Study 1; NCT02740972).

Study 1 was a multicenter, 2-period, dose-finding study conducted in the United States and Canada. During the initial period (first 4 weeks) of Study 1, patients were randomized (double blind) to VILTEPSO™ or placebo. All patients then received 20 weeks of open-label VILTEPSO™ 40 mg/kg once weekly (0.5 times the recommended dosage) (N=8) or 80 mg/kg once weekly (N=8). Study 1 enrolled ambulatory male patients 4 years to less than 10 years of age (median age 7 years) on a stable corticosteroid regimen for at least 3 months.

Efficacy was assessed based on change from baseline in dystrophin protein level (measured as % of the dystrophin level in healthy subjects, i.e., % of normal) at Week 25. Muscle biopsies (left or right biceps brachii) were collected from patients at baseline and following 24 weeks of VILTEPSO™ treatment, and analyzed for dystrophin protein

level by Western blot normalized to myosin heavy chain (primary endpoint) and mass spectrometry (secondary endpoint).

In patients who received VILTEPSO™ 80 mg/kg once weekly, 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, with a mean change in dystrophin of 5.3% (SD 4.5) of normal levels (p=0.01) as assessed by validated Western blot (normalized to myosin heavy chain); the median change from baseline was 3.8%. All patients demonstrated an increase in dystrophin levels over their baseline values. As assessed by mass spectrometry (normalized to filamin C), mean dystrophin levels increased from 0.6% (SD 0.2) of normal at baseline to 4.2% (SD 3.7) of normal by Week 25, with a mean change in dystrophin of 3.7% (SD 3.8) of normal levels (nominal p=0.03, not adjusted for multiple comparisons); the median change from baseline was 1.9%.

Safety

ADVERSE EVENTS

The most common adverse reactions (incidence ≥15% in patients treated with VILTEPSO™) were upper respiratory tract infection, injection site reaction, cough, and pyrexia.

WARNINGS & PRECAUTIONS

Kidney Toxicity: Based on animal data, may cause kidney toxicity. Kidney function should be monitored; creatinine may not be a reliable measure of renal function in DMD patients.

CONTRAINDICATIONS

None

Clinical Pharmacology

MECHANISMS OF ACTION

VILTEPSO™ is designed to bind 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

ADULTS

Duchenne muscular dystrophy: IV: 80 mg/kg once weekly.

PEDIATRICS

Children and Adolescents: IV: 80 mg/kg/dose once weekly. Note: DMD primarily affects males, and rarely females; therefore, clinical trial experience is limited to the male population.

GERIATRICS

DMD is largely a disease of children and young adults; therefore, there is no geriatric experience with VILTEPSO™ (Refer to adult dosing).

RENAL IMPAIRMENT

There are no dosage adjustments provided in the manufacturer's labeling (has not been studied). Viltolarsen is mainly excreted unchanged in the urine and renal impairment may increase exposure. However, creatinine is not a reliable measurement of kidney function due to the reduced skeletal mass in patients with Duchenne muscular dystrophy (DMD) so no specific dosage adjustment can be recommended based on eGFR; closely monitor patients with known renal impairment.

HEPATIC IMPAIRMENT

There are no dosage adjustments provided in the manufacturer's labeling; however, viltolarsen is not hepatically eliminated.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: 250 mg/5 mL (50 mg/mL) in a single-dose vial.