PDL DRUG REVIEW

Proprietary Name: Evrysdi®
Common Name: risdiplam
PDL Category: Muscular Atrophy Agents

Comparable Products	Preferred Drug List Status
Spinraza	Medical Coverage

Summary

Pharmacology/Usage: Risdiplam, the active ingredient of Evrysdi®, is a survival of motor neuron 2 (SMN2) splicing modifier designed to treat patients with spinal muscular atrophy (SMA) caused by mutations in chromosome 5q that lead to SMN protein deficiency. Risdiplam was demonstrated to increase exon 7 inclusion in SMN2 messenger ribonucleic acid (mRNA) transcripts and production of full-length SMN protein in the brain.

Indication: For the treatment of spinal muscular atrophy (SMA) in patients 2 months of age and older.

There is no pregnancy category for this product; however, the risk summary indicates that there are no adequate data on the developmental risk associated with the use of Evrysdi® in pregnant women. Pregnancy testing is recommended for females of reproductive potential prior to starting Evrysdi® and it may cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with Evrysdi® and for at least 1 month after the last dose. The safety and efficacy of use in the pediatric population below the age of 2 months have not been established.

Dosage Form: Oral Solution: 60mg powder for constitution. Following constitution, the volume of the solution is 80ml, providing 60mg/80ml (0.75mg/ml) risdiplam.

Recommended Dosage: Evrysdi® powder must be constituted to the oral solution by a pharmacist prior to dispensing to the patient. Keep the constituted oral solution in the original amber bottle to protect from light. Store in the refrigerator and discard any unused portion 64 days after constitution.

It is recommended that a healthcare provider discuss with the patient or caregiver how to prepare the prescribed daily dose prior to the administration of the first dose. Patients or caregivers should be instructed to prepare the dose using the reusable oral syringe provided. Evrysdi® must be taken immediately after it is drawn up in the oral syringe. If it is not taken within 5 minutes, Evrysdi® should be discarded from the oral syringe and a new dose should be prepared.

A dose should be administered orally once daily after a meal at about the same time each day. In infants who are breastfed, Evrysdi® should be administered after breastfeeding. Evrysdi® cannot be fixed with formula or milk. Patients should drink water after taking Evrysdi® to ensure the drug has been completely swallowed. If the patient is not able to swallow and has a nasogastric or gastrostomy tube, Evrysdi® can be administered via the tube. The tube should be flushed with water after delivering Evrysdi®.

Evrysdi® is to be administered orally once daily, with the recommended dosage determined by age and body weight. Refer to the table below, which was adapted from the prescribing information.

Age and Body Weight	Recommended Daily Dosage
2 months to < 2 years of age	0.2mg/kg
≥2 years of age weighing <20kg	0.25mg/kg
≥2 years weighing ≥20kg	5mg

If a dose is missed, Evrysdi® should be administered as soon as possible if still within 6 hours of the missed dose, and the usual dosing schedule can be resumed on the next day. Otherwise, the missed dose should be skipped, and the next dose should be taken at the regularly scheduled time on the next dose. If a dose is not fully swallowed or vomiting occurs after taking a dose, another dose should not be administered to make up for the lost dose. The patient should wait until the next day to take the next dose at the regularly scheduled time.

The safety and efficacy of use in patients with hepatic impairment have not been studied. Risdiplam is mainly metabolized by the liver, thus hepatic impairment may potentially increase the exposures to risdiplam. Avoid use of Evrysdi® in patients with impaired hepatic function.

Drug Interactions: Based on in vitro data, Evrysdi® may increase plasma concentrations of drugs eliminated via MATE1 or MATE2-K, such as metformin. Avoid coadministration of Evrysdi® with MATE substrates. If coadministration cannot be avoided, monitor for drug-related toxicities and consider dosage reduction of the co-administered drug (based on the labeling of that drug) if needed.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Evrysdi®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included fever (includes pyrexia and hyperpyrexia; 5%), diarrhea (9%), rash (15%), mouth and aphthous ulcers (7%), arthralgia (5%), and urinary tract infection (includes urinary tract infection and cystitis; 5%). Rash includes the terms rash, erythema, rash maculo-papular, rash erythematous, rash papular, dermatitis allergic, and folliculitis.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Genentech, A member of the Roche Group

Analysis: The efficacy of Evrysdi® for the treatment of patients with infantile-onset and later-onset spinal muscular atrophy (SMA) was assessed in 2 clinical studies. The overall findings of these studies support the effectiveness of Evrysdi® in SMA patients 2 months of age and older and appear to support the early initiation of treatment with Evrysdi®.

Study 1, the *infantile-onset SMA* study, was an open-label, 2-part study to assess the safety, efficacy, pharmacokinetics, and pharmacodynamics of Evrysdi® in patients with Type 1 SMA (symptom onset between 28 days and 3 months of age). Part 1 of Study 1 (N=21) provides efficacy and safety data in patients with Type 1 SMA. Additional safety information is provided by part 2 of Study 1 (N=41) in patients with Type 1 SMA. In part 1 of Study 1, patients were enrolled in one of two dosage cohorts. Patients in the higher-dosage cohort (N=17) had their dosage adjusted to the recommended dosage of 0.2mg/kg/day before 12 months of treatment, while patients in the low-dosage cohort (N=4) did not.

Effectiveness was established based on the ability to sit without support for at least 5 seconds (as measured by Item 22 of the Bayley Scales of Infant and Toddler Development- 3rd Edition [BSID-III] gross motor scale) and on the basis of survival without permanent ventilation. Permanent ventilation was defined as requiring a tracheostomy or more than 21 consecutive days of either non-invasive ventilation (≥16 hours per day) or intubation, in the absence of an acute reversible event.

The median age of onset of clinical signs and symptoms of Type 1 SMA in patients enrolled in part 1 of Study 1 was 2.0 months (range 0.9 to 3.0), while 71% were female and 81% were Caucasian. The median age at enrollment was 6.7 months and the median time between onset of symptoms and first dose was 4.0 months. All patients had genetic confirmation of homozygous deletion or compound heterozygosity predictive of loss of function of the SMN1 gene, and two SMN2 gene copies.

In part 1 of Study 1, the median duration of Evrysdi® treatment was 14.8 months (range 0.6 to 26.0), and 19 patients were treated for a minimum duration of 12 months. Of the patients who were treated with the recommended dosage of Evrysdi® of 0.2mg/kg/day, 41% (N=7/17) were able to sit independently for ≥5 seconds (BSID-III, Item 22) after 12 months of treatment. These results indicate a clinically meaningful deviation from the natural history of untreated infantile-onset SMA. As described in the natural history of untreated infantile-onset SMA, patients would not be expected to attain the ability to sit independently, and no more than 25% of these patients would be expected to survive without permanent ventilation beyond 14 months of age. After 12 months of treatment with Evrysdi®, 90% (N=19/21) of patients were alive without permanent ventilation (and reached 15 months of age or older). After a minimum of 23 months of treatment with Evrysdi®, 81% (N=17/21) of all patients were alive without permanent ventilation (and reached an age of 28 months or older; median 32 months; range 28 to 45 months).

Study 2, *later-onset SMA study*, was a 2-part, multicenter trial to assess the safety, efficacy, pharmacokinetics, and pharmacodynamics of Evrysdi® in patients diagnosed with SMA Type 2 or Type 3. Part 1 of Study 2 was dose-finding and exploratory in 51 patients (14% ambulatory). Part 2 was randomized, double-bind, placebo-controlled, and is described below.

The primary endpoint in part 2 of Study 2 was the change from baseline to month 12 in the Motor Function Measure 32 (MFM32) score. A key secondary endpoint was the proportion of patients with a 3-point or greater change from baseline to month 12 in the MFM32 total score. The MFM32 measures motor function abilities that relate to daily functions. The total MFM32 score is expressed as a percentage (range 0 to 100) of the maximum possible score, with higher scores indicating greater motor function. Another key secondary endpoint was the Revised Upper Limb Module (RULM). The RULM is a tool used to assess motor performance of the upper limb in SMA patients. It tests proximal and distal motor functions of the arm. The total score ranges from 0 (all the items cannot be performed) to 37 (all the activities are achieved fully without any compensatory maneuvers).

Part 2 of Study 2 enrolled 180 non-ambulatory patients with Type 2 (71%) or Type 3 (29%) SMA. Patients were randomized to receive Evrysdi® at the recommended dosage or placebo, and randomization was stratified by age group (2 to 5, 6 to 11, 12 to 17, or 18 to 25 years of age). The median age of patients at the start of treatment was 9.0 years (range 2 to 25) and the median time between onset of initial SMA symptoms and first treatment was 102.6 months (range 1 to 275). Of the 180 patients included in the trial, 51% were female and 67% were Caucasian. At baseline, 67% of patients had scoliosis (32% of them with severe scoliosis). In addition, patients had a mean baseline MFM32 score of 46.1 and RULM score of 20.1. Overall, baseline demographic characteristics were reasonably balanced between the treatment groups (Evrysdi® and placebo), with the exception of scoliosis (63% in the Evrysdi® arm vs 73% in the placebo group).

The primary analysis on the change from baseline in MFM32 total score at month 12 demonstrated a clinically meaningful and statistically significant difference between patients treated with Evrysdi® and placebo. Results can be seen in the table below, which was adapted from the prescribing information.

Endpoint	Evrysdi® (N=120)	Placebo (N=60)
Primary Endpoint:		
Change from baseline in total MFM32 score at month 12, least square (LS) means	1.36	-0.19
Difference from placebo, p-value	1.55; p=0.0156	
Secondary Endpoints:		
Proportion of patients with a change from baseline MFM32 total score of 3 or more, at month 12	38.3%	23.7%
Odds ratio for overall response; Adjusted (unadjusted) p-value	2.35; p=0.0469 (0.0469)	
NNT calculated by CHC	7	
Change from baseline in total score of RULM at month 12, LS means	1.61	0.02
Difference from placebo; Adjusted (unadjusted) p-value	1.59; p=0.0469 (0.0028)	

Place in Therapy: Evrysdi® is a powder for oral solution indicated for the treatment of spinal muscular atrophy (SMA) in patients 2 months of age and older. It is the first oral agent FDA approved to treat this disease. It was studied in both infantile-onset and later-onset SMA. In the infantile-onset SMA study, after a minimum of 23 months of Evrysdi® treatment, 81% of all patients (N=17/21) were alive without permanent ventilation. In addition, 41% treated with Evrysdi® were able to sit independently for ≥5 seconds after 12 months of treatment. These results are superior to the natural history of the disease. In the later-onset SMA study, the change from baseline in MFM32 total score at month 12 demonstrated a clinically meaningful and statistically significant difference between patients treated with Evrysdi® and placebo, favoring Evrysdi®.

It is recommended that Evrysdi® should be non-preferred with conditions in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement:
- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☒ **Refer to DUR for PA Criteria**

References

[1] Evrysdi [package insert]. South San Francisco, CA: Genentech, Inc., A Member of the Roche Group; 2020.