

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrEVRYSDI®

Risdiplam Powder for Oral Solution

60 mg/bottle (0.75 mg/mL after reconstitution), Oral or Enteral

Other drugs for disorders of the musculo-skeletal system

ATC code: M09AX10

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RECENT MAJOR LABEL CHANGES

WARNINGS AND PRECAUTIONS (7) Skin, Cutaneous Vasculitis

12-2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

EVRYSDI (risdiplam) is indicated for the treatment of spinal muscular atrophy (SMA) in patients 2 months and older.

Adult: There are limited data on EVRYSDI for patients over 25 years of age.

1.1 Pediatrics

Pediatrics (≥ 2 months): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of EVRYSDI in pediatric patients 2 months or older has been established; therefore, Health Canada has authorized an indication for pediatric use.

In the limited number of patients aged 2 to 5 months receiving the recommended dose in the clinical trials (see [14 CLINICAL TRIALS](#)), higher exposures are predicted at that dose (see [10.3 Pharmacokinetics](#)), further narrowing the safety margins in this age group (see [16 NON-CLINICAL TOXICOLOGY](#)).

No data are available in infants below 2 months of age; therefore, EVRYSDI is not indicated in this patient population.

1.2 Geriatrics

Geriatrics (> 60 years of age): EVRYSDI has not been studied in patients with SMA above 60 years of age (see [7 WARNINGS AND PRECAUTIONS](#), [7.1 Special Populations](#), [7.1.4 Geriatrics](#) and [10.3 Pharmacokinetics](#), Special Populations and Conditions).

2 CONTRAINDICATIONS

EVRYSDI is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see [6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING](#).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

EVRYSDI oral solution must be reconstituted by a health professional prior to being dispensed.

4.2 Recommended Dose and Dosage Adjustment

EVRYSDI is taken orally once daily after a meal, using the re-usable oral syringe provided, at approximately the same time each day. In infants who are breastfed, EVRYSDI should be administered after breast-feeding.

The recommended once daily dose of EVRYSDI for SMA patients is determined by age and body weight (see Table 1).

Table 1 Dosing Regimen by Age and Body Weight

<i>Age and Body Weight</i>	<i>Recommended Daily Dose</i>
2 months to < 2 years of age	0.20 mg/kg
≥ 2 years of age (< 20 kg)	0.25 mg/kg
≥ 2 years of age (≥20 kg)	5 mg

Dose changes must be made under the supervision of a health professional.

Treatment with a daily dose above 5 mg has not been studied.

No data are available in infants below 2 months of age.

Special Dosage Instructions

Pediatric use

In the limited number of patients aged 2 to 5 months receiving the recommended dose in the clinical trials (see [14 CLINICAL TRIALS](#)), higher exposures are predicted at that dose (see [10.3 Pharmacokinetics](#)), further narrowing the safety margins in this age group (see [16 NON-CLINICAL TOXICOLOGY](#)).

Geriatric use

The impact of geriatric age on the pharmacokinetics of EVRYSDI has not been studied (see [7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.4 Geriatrics](#) and [10.3 Pharmacokinetics, Special Populations and Conditions](#)).

Renal Impairment

No dose adjustment is required in patients with renal impairment (see [7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, Renal](#) and [10.3 Pharmacokinetics](#)).

Hepatic Impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment. Severe hepatic impairment has not been studied and could lead to increased EVRYSDI exposure (see [7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, Hepatic](#) and [10.3 Pharmacokinetics](#)).

4.3 Reconstitution

Please consult the Instructions for Reconstitution and Instructions for Use provided in the Patient Medication Information section for detailed instructions for reconstitution and administration.

Preparation of the 60 mg EVRYSDI Powder for Oral solution (0.75 mg/mL)

Caution should be exercised in the handling of EVRYSDI powder for oral solution (see [12 SPECIAL HANDLING INSTRUCTIONS](#)). Avoid inhalation and direct contact with skin or mucous membranes with the dry powder and the reconstituted solution. Wear disposable gloves during reconstitution and while wiping the outer surface of the bottle/cap and cleaning

the working surface after reconstitution. If contact occurs, wash thoroughly with soap and water; rinse eyes with water.

Selecting the Oral Syringe for the Prescribed Daily Dose

Table 2 Selecting the Oral Syringe for the Prescribed Daily Dose of EVRYSDI

Dose Strength	Syringe Size	Dosing Volume	Syringe Increments
0.75 mg/mL (100 mL bottle)	6 mL	1.0 to 6.0 mL	0.1 mL
	12 mL	6.2 to 6.6 mL	0.2 mL

For the calculation of dosing volume, the syringe increments need to be considered. Round the dose volume to the closest increment marked on the selected oral syringe.

Use Purified Water or Water for Injection (WFI) to reconstitute the medicine.

Mix 79 mL of Purified Water or Water for Injection (WFI) into the medicine bottle.

Patients should take EVRYSDI immediately after it is drawn up into the oral syringe. If it is not taken within 5 minutes, the dose should be discarded and a new dose should be prepared.

No incompatibilities between EVRYSDI and the recommended oral syringes have been observed.

4.4 Administration

Use the re-usable oral syringe provided to deliver the daily dose of EVRYSDI. It is recommended that a Health Professional discuss with the patient or caregiver how to prepare the prescribed daily dose prior to administration of the first dose.

The patient should drink water after taking EVRYSDI to ensure the drug has been completely swallowed. Do not mix EVRYSDI with formula or milk. If the patient is unable to swallow and has a nasogastric or gastrostomy tube, administer EVRYSDI via the tube. The tube should be flushed with water after delivering EVRYSDI.

4.5 Missed Dose

EVRYSDI is taken orally once daily at approximately the same time each day. If a dose of EVRYSDI is missed, administer as soon as possible if still within 6 hours of the scheduled missed dose. Otherwise, skip the missed dose and take the next dose at the regularly scheduled time the next day.

If a dose is not fully swallowed or vomiting occurs after taking a dose of EVRYSDI, do not administer another dose to make up for the incomplete dose. Wait until the next day to administer the next dose at the regularly scheduled time.

5 OVERDOSAGE

There is little experience with overdosage of EVRYSDI in clinical trials. There is no known antidote for overdosage of EVRYSDI.

In case of overdosage, the patient should be closely supervised and supportive care instituted.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3 – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral or enteral	powder for solution 60 mg/bottle (0.75 mg/mL after reconstitution)	ascorbic acid, disodium edetate dihydrate, isomalt, macrogol/ polyethylene glycol 6000, mannitol, sodium benzoate, strawberry flavor, sucralose, tartaric acid

EVERYSDI (risdiplam) is available as a powder for solution in an amber glass bottle and closed with a child-resistant and tamper-evident screw cap.

Each EVERYSDI carton contains one 100 mL bottle.

7 WARNINGS AND PRECAUTIONS

General

For patients who are fructose/sugar intolerant, there is a potential for exceeding maximum daily recommendation for fructose/sugar with the recommended dosing regimen.

Dependence/Tolerance

EVERYSDI has no known potential to lead to abuse and dependence.

Dosing in Patients aged 2-5 months

In the limited number of patients aged 2 to 5 months receiving the recommended dose in the clinical trials (see [14 CLINICAL TRIALS](#)), higher exposures are predicted at that dose (see [10.3 Pharmacokinetics](#)), further narrowing the safety margins in this age group (see [16 NON-CLINICAL TOXICOLOGY](#)).

Driving and Operating Machinery

EVERYSDI has no known influence on the ability to drive and use machines.

Hepatic Impairment

The pharmacokinetics of a single dose of 5 mg EVERYSDI were evaluated in adult subjects with mild or moderate hepatic impairment, with no significant impact observed. No dose adjustment is therefore required in patients with mild or moderate hepatic impairment. Severe hepatic impairment has not been studied and could lead to increased EVERYSDI exposure (see sections [4.2 Recommended Dose and Dosage Adjustment](#) and [10.3 Pharmacokinetics, Special Populations and Conditions](#)).

Ophthalmologic

The effects of EVERYSDI on retinal structure observed in the non-clinical safety studies (including irreversible photoreceptor degeneration) have not been observed in clinical studies with SMA patients. However, long-term data are limited. The long-term clinical relevance of these non-clinical findings has therefore not been established (see [16 NON-](#)

CLINICAL TOXICOLOGY and 9.4 Drug-Drug Interactions, Concomitant use with retinotoxic drugs not studied).

Renal Impairment

EVERYSDI has not been studied in renal impairment. Renal impairment is not expected to alter the exposure to risdiplam (see 4.2 Recommended Dose and Dosage Adjustment and 10.3 Pharmacokinetics, Metabolism, Elimination and Special Populations and Conditions).

Reproductive Health: Female and Male Potential

- Fertility

Male patients

Due to reversible effects of EVERYSDI on male fertility based on observations from animal studies, male patients should not donate sperm while on treatment and for 4 months after the last dose of EVERYSDI (see 16 NON-CLINICAL TOXICOLOGY).

Male fertility may be compromised while on treatment with EVERYSDI based on non-clinical findings. In rat and monkey reproductive organs, sperm degeneration and reduced sperm numbers were observed (see 16 NON-CLINICAL TOXICOLOGY). The effects on sperm cells are expected to be reversible upon discontinuation of EVERYSDI. Prior to initiating treatment with EVERYSDI, fertility preservation strategies should be discussed with male patients receiving EVERYSDI. Male patients may consider sperm preservation, prior to treatment initiation or after a treatment free period of at least 4 months. Male patients who wish to father a child should stop treatment with EVERYSDI for a minimum of 4 months. Treatment can be re-started after conception.

Female patients

Based on non-clinical data, an impact of EVERYSDI on female fertility is not expected (see 16 NON-CLINICAL TOXICOLOGY).

Embryo-fetal toxicity has been observed in animal studies (see 16 NON-CLINICAL TOXICOLOGY). Patients of reproductive potential must be informed of the risks and must use highly effective contraception.

Contraception

Male and female patients of reproductive potential must adhere to the following contraception requirements:

- Female patients of childbearing potential must use highly effective contraception during treatment with EVERYSDI and for at least 1 month after the last dose.
- Male patients and their female partners of childbearing potential must both use highly effective contraception during treatment with EVERYSDI and for at least 4 months after his last dose.

Pregnancy testing

The pregnancy status of females of reproductive potential should be verified prior to initiating EVERYSDI therapy. Pregnant women must be clearly advised of the risk of harm to the fetus.

Skin

Cutaneous Vasculitis

Cutaneous vasculitis was identified from post-marketing experience, as a single case with no systemic involvement and mild sequelae. There were two positive dechallenges, and a positive rechallenge, with the rechallenge occurring when there was no other ongoing

treatment. Symptoms resolved after permanent discontinuation of EVRYSDI (see also 8.5 Post-Market Adverse Reactions).

7.1 Special Populations

7.1.1 Pregnant Women

There are no clinical data from the use of EVRYSDI in pregnant women. EVRYSDI has been shown to be embryo-fetotoxic and teratogenic in animals. Based on the findings from animal studies, EVRYSDI crosses the placental barrier and may cause fetal harm (see [16 NON-CLINICAL TOXICOLOGY](#)).

EVRYSDI should not be used during pregnancy unless the benefit to the mother outweighs the potential risks to the fetus. If a pregnant woman needs to be treated with EVRYSDI, she must be clearly advised on the potential risk to the fetus.

The safe use of EVRYSDI during labour and delivery has not been established.

7.1.2 Breast-feeding

It is not known whether EVRYSDI is excreted in human breast milk. Precaution should be exercised because many drugs can be excreted in human milk. Studies in rats show that EVRYSDI is excreted into milk (see [16 NON-CLINICAL TOXICOLOGY](#), Reproductive and Developmental Toxicity) and that EVRYSDI milk:plasma ratio was >3 for at least 24 hours following dosing. As the potential for harm to the nursing infant is unknown, a decision must be made with the patient's treating physician. It is recommended not to breastfeed during treatment with EVRYSDI.

7.1.3 Pediatrics

Pediatrics (> 2 months): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of EVRYSDI in pediatric patients 2 months or older has been established; therefore, Health Canada has authorized an indication for pediatric use.

In the limited number of patients aged 2 to 5 months receiving the recommended dose in the clinical trials (see [14 CLINICAL TRIALS](#)), higher exposures are predicted at that dose (see [10.3 Pharmacokinetics](#)), further narrowing the safety margins in this age group (see [16 NON-CLINICAL TOXICOLOGY](#)).

The safety and efficacy of EVRYSDI in pediatric patients < 2 months of age have not been established (see section [14 CLINICAL TRIALS](#)).

7.1.4 Geriatrics

EVRYSDI has not been studied in patients with SMA above 60 years of age (see sections [10.3 Pharmacokinetics](#), Special Populations and Conditions and [14 CLINICAL TRIALS](#)).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety profile of EVRYSDI is based on the FIREFISH and SUNFISH studies; and a supportive study, JEWELFISH.

The most commonly reported adverse reactions related to EVRYSDI in infantile-onset SMA patients were upper respiratory tract infections (82%); pyrexia (55%); lower respiratory tract infections (53%); rash (29%); constipation (26%); diarrhea (19%); vomiting (18%); cough (13%); eczema (13%); and urinary tract infection (6%).

In later-onset SMA, the most commonly reported adverse reactions related to EVRYSDI were pyrexia (22%); diarrhea (17%); rash (17%); mouth/aphthous ulcer (7%); urinary tract infection (7%); and arthralgia (5%).

Deaths occurred in 9.7% of patients with infantile-onset SMA on treatment with EVRYSDI and were due to progression of underlying SMA. No deaths occurred in patients with later-onset SMA.

Adverse events (regardless of causality) led to permanent discontinuation of EVRYSDI in one patient with a fatal viral respiratory tract infection in infantile-onset SMA. In infantile-onset SMA, dose was interrupted for single events of hypoxia, pneumonia and pyrexia.

In later-onset SMA, dose was interrupted for single events of gastroenteritis, pharyngitis, upper respiratory tract infection, varicella, constipation, vomiting, physical deconditioning, pyrexia, traumatic shock and aspiration.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The SUNFISH study is a two-part study with later-onset SMA between 2-25 years of age (see [14 CLINICAL TRIALS, 14.1 Trial Design and Study Demographics](#)). The adverse drug reactions (ADR) observed in clinical trials for later-onset SMA in Table 4 are based on SUNFISH Part 2 (n=180), the randomized double-blind, placebo-controlled portion with a follow-up duration of at least 12 months.

Table 4 Summary of adverse drug reactions for later-onset SMA patients observed in $\geq 5\%$ of Patients Treated with EVRYSDI and with an Incidence $\geq 5\%$ Greater Than on Placebo in SUNFISH Part 2 study

	EVRYSDI N=120 n (%)	Placebo N=60 n (%)
Gastrointestinal Disorders		
Diarrhea	20 (17)	5 (8)
Mouth and aphthous ulceration	8 (7)	0
General disorders and administration site conditions		
Pyrexia ¹	26 (22)	10 (17)
Infections and infestations		
Urinary tract infection ²	8 (7)	0
Musculoskeletal and connective tissue disorders		
Arthralgia	6 (5)	0
Skin and Subcutaneous Tissue Disorders		
Rash ³	20 (17)	1 (2)

¹ Includes pyrexia and hyperpyrexia

² Includes cystitis and urinary tract infection

³ Includes rash, rash maculo-papular, erythema, dermatitis allergic, rash erythematous, folliculitis, rash papular

The FIREFISH study is a two-part, open-label study that enrolled 62 patients with infantile-onset SMA between 2.2 and 6.9 months of age. Fifty-seven patients received EVRYSDI treatment for more than 12 months (range: 18 days – 47 months) (see [14 CLINICAL TRIALS, 14.1 Trial Design and Study Demographics](#)). The adverse drug reactions (ADRs) observed in clinical trials for infantile-onset SMA in Table 3 are based on the pooled analysis of patients from FIREFISH Part 1 and 2.

Table 5 Summary of adverse drug reactions for infantile-onset SMA patients observed in FIREFISH (Part 1 and 2) study in ≥ 5%

	Incidence N=62 n (%)	Number of events/ 100 patient years Total exposure in patient years = 142.4
Gastrointestinal Disorders		
Constipation	16 (26)	17.6
Diarrhea	12 (19)	9.8
Vomiting	11 (18)	16.9
General disorders and administration site conditions		
Pyrexia	34 (55)	74.4
Infections and infestations		
Upper respiratory tract infection ¹	51 (82)	95.5
Lower respiratory tract infection ²	33 (53)	44.2
Cough	8 (13)	7.7
Urinary tract infection	4 (6)	4.2
Skin and Subcutaneous Tissue Disorders		
Rash ³	18 (29)	16.2
Eczema ⁴	8 (13)	6.3

¹ Includes upper respiratory tract infection (bacterial, viral or not specified), nasopharyngitis, rhinitis, influenza, respiratory tract infection (viral or not specified), pharyngitis, COVID-19

² Includes pneumonia (bacterial, staphylococcal, viral or not specified), bronchitis, bronchiolitis, lower respiratory tract infection (viral or not specified), COVID-19, respiratory syncytial virus bronchiolitis, tracheitis, tracheobronchitis, pneumonia aspiration

³ Includes rash, rash maculo-papular, erythema, dermatitis, dermatitis allergic, rash papular, dermatitis acneiform, folliculitis

⁴ Includes eczema, dyshidrotic eczema, eczema nummular, dermatitis atopic, dermatosis

In both infantile-onset and later-onset SMA patients, the adverse reactions diarrhea and rash occurred without an identifiable time or clinical pattern and resolved despite ongoing treatment with EVRYSDI.

Safety Profile in Patient Previously Treated for SMA

A supportive study JEWELFISH, consisted of 76 patients previously treated with nusinersen and 14 patients previously treated with onasemnogene abeparvovec. The safety profile of EVRYSDI in treating non-naïve patients in the JEWELFISH study is consistent with the safety profile of EVRYSDI in treating naïve SMA patients treated in the FIREFISH (Part 1 and Part 2) and SUNFISH (Part 1 and Part 2) studies.

8.3 Less Common Clinical Trial Adverse Reactions

Patients with Infantile onset SMA (FIREFISH study):

Gastrointestinal Disorders: aphthous ulcer

8.5 Post-Market Adverse Reactions

The following adverse drug reaction has been identified from postmarketing experience with EVRYSDI (Table 6). Adverse drug reaction is listed according to system organ classes in MedDRA. See also 7 WARNINGS AND PRECAUTIONS, Skin.

Table 6 Adverse drug reactions from postmarketing experience

System Organ Class	Adverse Reaction	Frequency Category
Skin and subcutaneous disorders	Cutaneous vasculitis ¹	Unknown

¹ Incidence rate and frequency category cannot be estimated based on available data

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Risdiplam is primarily metabolized by flavin monooxygenase 1 and 3 (FMO1 and 3), and also by cytochrome P450 enzymes (CYPs) 1A1, 2J2, 3A4 and 3A7. Risdiplam is a weak substrate of human multidrug resistance protein 1 (MDR1) and human breast-cancer-resistant protein (BCRP) *in vitro*. Human MDR-1 or BCRP inhibitors are not expected to result in a clinically significant increase of risdiplam concentrations.

9.4 Drug-Drug Interactions

Concomitant use with retinotoxic drugs not studied

The potential for synergistic effects of concomitant administration of risdiplam with retinotoxic drugs has not been studied. Therefore, caution in using concomitant medications with known or suspected retinal toxicity is recommended (see 7 WARNINGS AND PRECAUTIONS, Ophthalmologic).

Concomitant administration with other SMA therapies

The concomitant use of risdiplam and nusinersen should be avoided as there is no efficacy or safety data to support such use. Regarding the safety and efficacy of risdiplam in patients that previously received SMN1 gene therapy: there are limited safety data in these patients (see 8.2 Clinical Trial Adverse Reactions), while efficacy of risdiplam in this context has not been established.

Table 7

Name	Source of Evidence	Effect	Clinical comment
Itraconazole and other CYP3A inhibitors	CT	↑ risdiplam Not clinically significant	Co-administration of 200 mg itraconazole twice daily, a strong CYP3A inhibitor, with a single oral dose of 6 mg risdiplam did not exhibit a clinically relevant effect on the pharmacokinetic (PK) of risdiplam (11% increase in AUC, 9% decrease in C _{max}). No dose adjustments are required when EVRYSDI is co-administered with a CYP3A inhibitor.

Midazolam, and other CYP3A substrates	CT	↑ midazolam Not clinically significant	Risdiplam is a weak inhibitor of CYP3A <i>in vitro</i> . In healthy adult subjects, administration of EVRYSDI once daily for 2 weeks slightly increased the exposure of midazolam, a sensitive CYP3A substrate (AUC 11%; C _{max} 16%). The extent of the interaction is not considered clinically relevant, and therefore no dose adjustment is required for CYP3A substrates.
Multidrug and Toxin Extrusion (MATE) Transporter Substrates (e.g., metformin)	T	↑ MATE1 and MATE2-K	Risdiplam and its major metabolite are <i>in vitro</i> inhibitors of the human organic cation transporter 2 (OCT2) and the multidrug and toxin extrusion (MATE)1 and MATE2-K transporters. At therapeutic drug concentrations, no interaction is expected with OCT2 substrates. Based on <i>in vitro</i> data, EVRYSDI may increase plasma concentrations of drugs eliminated via MATE1 or MATE2-K, such as metformin. The clinical relevance of the co-administration with MATE1/2-K substrates is unknown, as such drugs were prohibited per protocol in the clinical studies. If co-administration cannot be avoided, monitor for drug-related toxicities, and consider dosage reduction of the co-administered drug if needed (based on labelling of that drug).

Legend: CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 ACTION AND CLINICAL PHARMACOLOGY

10.4 Mechanism of Action

Risdiplam is a pre-mRNA splicing modifier of survival of motor neuron 2 (SMN2) designed to treat SMA, which is caused by mutations in chromosome 5q that lead to SMN protein deficiency. Functional SMN protein deficiency is the pathophysiological mechanism of all SMA types. Risdiplam shifts the balance from exon 7 exclusion to exon 7 inclusion into the mRNA transcript, leading to increased production in functional and stable SMN protein. Thus, risdiplam treats SMA by increasing and sustaining functional SMN protein levels.

10.5 Pharmacodynamics

In non-clinical species, risdiplam distributes broadly in the body, including the central nervous system (CNS), and thereby leading to SMN protein increase in homogenates from brain and quadriceps muscle. In non-clinical species, concentrations of risdiplam in plasma and SMN protein in blood reflect its distribution and pharmacodynamic effects in tissues such as brain and muscle.

In all clinical trials, risdiplam led to a consistent and durable increase in SMN protein with a greater than 2-fold median change from baseline within 4 weeks of treatment initiation as measured in blood. This increase in SMN protein was sustained throughout the treatment period of up to 2 years for infantile-onset SMA and later-onset SMA patients (see [14 CLINICAL TRIALS, 14.2 Study Results](#)).

Secondary Pharmacodynamics

In vitro and *in vivo* data indicate that risdiplam may cause alternative splicing of additional genes, including FOXM1 and MADD. FOXM1 and MADD are thought to be involved in cell cycle regulation and apoptosis, respectively, and have been identified as possible contributors to adverse effects seen in animals

10.6 Pharmacokinetics

Pharmacokinetic parameters for EVRYSDI have been characterized in healthy adult subjects and in patients with SMA.

After administration of EVRYSDI as an oral solution, pharmacokinetics of risdiplam were approximately linear between 0.6 and 18 mg in a single-ascending-dose study in healthy adult subjects, and between 0.02 and 0.25 mg/kg (up to 5 mg) once daily in a multiple-ascending-dose study in patients with SMA. Risdiplam's pharmacokinetics was best described by a population PK model with three-transit-compartment absorption, two-compartment disposition and first-order elimination. Body weight and age were found to have significant effect on the pharmacokinetics.

Following once-daily oral administration of risdiplam for 14 days in healthy subjects, approximately 3-fold accumulation of peak plasma concentrations (C_{max}) and area under the plasma concentration-time curve (AUC_{0-24h}) was observed. Risdiplam exposures reach steady state 7 to 14 days after once-daily administration.

The observed risdiplam exposure range in FIREFISH and SUNFISH was 1060 to 3800 ng·h/ml at the Month 12 visit after one year of treatment, based on the target mean AUC 2000 ng·h/ml. For AUC values within this range, the efficacy and safety of risdiplam are established. For AUC values outside this range, it is uncertain how efficacy and safety would change.

FIREFISH (2 - 7 months old at enrollment):

For the subset of infantile-onset SMA patients aged 2-5 months (n=25): A limited number of these patients received a daily dose of 0.2 mg/kg (see [14 CLINICAL TRIALS, 14.1 Trial Design and Study Demographics](#)). Therefore, the population-PK model was used to simulate the exposure in this sub-group following a dose of 0.2 mg/kg. The predicted mean AUC_{0-24h} on Day 28, after 4 weeks of treatment was 2870 ng·h/mL, with a 95% range of 1850-4800 ng·h/mL (corresponding to the 2.5th and 97.5th percentiles in this subgroup). For the dose of 0.08 mg/kg, the estimated exposure is too low.

For infantile-onset SMA patients > 5 months old (and < 2 years) (n=37): At the recommended daily dose of 0.2 mg/kg, the mean AUC_{0-24h} was estimated to be 2140 ng·h/mL with a range of 1300-3690 (corresponding to the 2.5th and 97.5th percentiles in this subgroup).

SUNFISH (2-25 years old at enrollment):

For later-onset SMA patients with a bodyweight < 20 kg (n=28): At the recommended daily dose of 0.25 mg/kg, the mean AUC_{0-24h} was estimated to be 2250 ng·h/mL with a range of 1650 – 3010 (corresponding to the 2.5th and 97.5th percentiles in this subgroup).

For later-onset SMA patients with a body weight ≥20 kg (n=89): At the recommended daily dose of 5 mg, the mean AUC_{0-24h} was estimated to be 2010 ng·h/mL with a range of 1250 – 3220 (corresponding to the 2.5th and 97.5th percentiles in this subgroup).

The observed maximum concentration (mean C_{max}) was between 194 ng/mL at 0.2 mg/kg in FIREFISH and 120 ng/mL in SUNFISH Part 2.

Absorption: Risdiplam was rapidly absorbed in the fasted state with a plasma t_{max} ranging from 1 to 4 hours after oral administration. Based on limited data (n = 3), food (high-fat, high calorie breakfast) had no relevant effect on the exposure of risdiplam. In the clinical efficacy studies, risdiplam was administered with a morning meal or after breastfeeding.

Distribution: The population pharmacokinetic parameter estimates were 98 L for the apparent central volume of distribution, 93 L for the peripheral volume, and 0.68 L/hour for the inter-compartment clearance.

Risdiplam is predominantly bound to serum albumin, without any binding to alpha-1 acid glycoprotein, with a free fraction of 11%.

Metabolism: Risdiplam is primarily metabolized by flavin monooxygenase 1 and 3 (FMO1 and FMO3), and also by CYPs 1A1, 2J2, 3A4 and 3A7.

Elimination: Population PK analyses estimated an apparent clearance (CL/F) of 2.6 L/h for risdiplam.

The effective half-life of risdiplam was approximately 50 hours in SMA patients.

Approximately 53% of the dose (14% unchanged risdiplam) was excreted in the feces and 28% in urine (8% unchanged risdiplam). Parent drug was the major component found in plasma, accounting for 83% of drug related material in circulation. The pharmacologically inactive metabolite M1 was identified as the major circulating metabolite.

Special Populations and Conditions

Pediatrics: Body weight and age were identified as significant covariates in the population PK analysis. The dose is therefore adjusted based on age (below and above 2 years) and body weight (up to 20 kg). No data are available in patients less than 2 months of age.

Geriatrics: The impact of geriatric age on the pharmacokinetics of EVRYSDI has not been studied.

Ethnic origin: There were no clinically significant differences seen in the pharmacokinetics of Japanese and Caucasian subjects.

Hepatic Insufficiency: After administration of a single oral 5 mg dose of risdiplam to adult subjects in a dedicated study, the mean ratios for C_{max} and AUC compared to healthy controls (n = 10) were: 0.95 and 0.80 in mild (Child-Pugh Class A; n=8), and 1.20 and 1.08 in moderate (Child-Pugh Class B; n=8) hepatic impaired subjects. Severe hepatic impairment has not been studied. Given the liver appears to be a primary site for metabolism of risdiplam, severe hepatic impairment could lead to increased exposure.

Renal Insufficiency: No studies have been conducted to investigate the pharmacokinetics of risdiplam in renal impairment. Elimination of risdiplam as unchanged entity via renal excretion is minor (8%). Renal impairment is not expected to alter the exposure to risdiplam.

11 STORAGE, STABILITY AND DISPOSAL

Keep in the original amber bottle. Store at room temperature (15 – 25°C).

After reconstitution, the oral solution should be stored in the refrigerator (2 to 8°C) for up to 64 days. Do not freeze. Keep the oral solution in the original bottle and keep the bottle always in an upright position with the cap tightly closed.

This medicine should not be used after the expiry date (“EXP”) for the powder, and “Discard After” for the reconstituted oral solution) written on the pack and on the bottle.

Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

Caution should be exercised in the handling of EVRYSDI powder for oral solution (see [4 DOSAGE AND ADMINISTRATION](#), [4.3 Reconstitution](#)). Avoid inhalation and direct contact with skin or mucous membranes with the dry powder and the reconstituted solution. Wear disposable gloves during reconstitution and while wiping the outer surface of the bottle/cap and cleaning the working surface after reconstitution. If contact occurs, wash thoroughly with soap and water; rinse eyes with water.

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment must be minimized. Medicines must not be disposed of via wastewater and disposal through household waste should be avoided.

Local requirements should be followed for the disposal process of unused/expired medicines.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

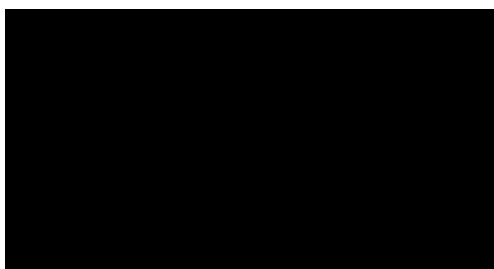
Drug Substance

Proper/Common name: risdiplam

Chemical name: 7-(4,7-Diazaspiro[2.5]octan-7-yl)-2-(2,8-dimethylimidazo[1,2-*b*]pyridazin-6-yl)-4*H*-pyrido-[1,2-*a*]pyrimidin-4-one

Molecular formula and molecular mass: C₂₂H₂₃N₇O, 401.46 g/mol

Structural formula:



Physicochemical properties: risdiplam is a light yellow or yellow or grayish yellow or greenish yellow powder or powder with lumps.

14 CLINICAL TRIALS

14.4 Trial Design and Study Demographics

Table 8 - Summary of patient demographics for clinical trials in spinal muscular atrophy

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
BP39055 (SUNFISH)	<p><u>Part 1:</u> A double-blind, placebo controlled, randomized, exploratory dose finding study in patients with Type 2 and Type 3 SMA (ambulant and non-ambulant) to select the dose for Part 2.</p>	<p>Oral, OD administration</p> <p><u>Part 1</u></p> <p>Age 12-25 years: 3 mg or 5 mg</p> <p>Age 2-11 years: 0.02, 0.05, 0.15 or 0.25 mg/kg</p> <p>Minimum of 12-weeks placebo-controlled treatment, after which patients on placebo switched to risdiplam at the dose tested in their cohort. After the dose selection for Part 2, all patients switched to the pivotal dose.</p>	<p><u>Part 1:</u></p> <p>51 patients</p> <p>2 - 11 years cohort (n = 31) and</p> <p>12 - 25 years cohort (n = 20)</p>	<p><u>Part 1:</u></p> <p>2 -11 years cohort: 5.2 (2-11) years and</p> <p>12 - 25 years cohort: 15.8 (12-24) years</p>	<p><u>Part 1:</u></p> <p>2 -11 years cohort: F: 45.2% M: 58.2%</p> <p>12 - 25 years cohort: F: 65.0% M: 35.0%</p>
	<p><u>Part 2:</u> A double-blind, randomized, placebo controlled, parallel design study to investigate the efficacy, safety, and tolerability of risdiplam in patients aged 2-25 years with Type 2 and non-ambulant Type 3 SMA.</p> <p><u>Parts 1 and 2</u> Following 24 months of treatment in each part, patients can enter an OLE phase.</p>	<p>Oral, OD administration</p> <p><u>Part 2</u></p> <p>Pivotal dose: 5 mg once daily for patients with a BW \geq 20 kg and 0.25 mg/kg once daily for patients with a BW <20 kg</p> <p>24-month treatment period (patients on placebo will be switched to active treatment in a blinded manner after 12 months).</p>	<p><u>Part 2:</u></p> <p>risdiplam: 120</p> <p>placebo: 60</p>	<p><u>Part 2:</u></p> <p>risdiplam: 9.9 (2-25) years</p> <p>placebo: 10.3 (2-24) years</p>	<p><u>Part 2:</u></p> <p>risdiplam: F: 50.8% M: 49.2%</p> <p>placebo: F/M: 50/50%</p>

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
BP39056 (FIREFISH)	Seamless, multi-center, two-part study in SMA Type 1 infants aged 1 to 7 months at the time of enrollment: <u>Part 1</u> : Open-label dose-escalation study to select the dose for Part 2.	OD oral administration <u>Part 1</u> Starting dose for first infant: 0.00106 mg/kg single dose. Once daily treatment with 0.0106, 0.04, 0.08, 0.2, 0.25 mg/kg. After selection of the starting dose for Part 2 the protocol was amended to switch all patients to the dose of 0.2 mg/kg. (Of the n = 6 subset of patients enrolled at < 5 months of age, n = 2 received 0.2 mg/kg for at least 7 days while < 5 months of age) Minimum of 4 weeks treatment for dose selection after which all patients continue to receive risdiplam until Month 24.	<u>Part 1</u> : 21 infants	<u>Part 1</u> : 5.8 (3.3-6.9) months	<u>Part 1</u> : F: 71.4% M: 28.6%

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
	<p><u>Part 2:</u> Open-label study to assess the efficacy, safety, and tolerability of risdiplam in infants with type 1 SMA.</p> <p><u>Parts 1 and 2</u> Following 24 months of treatment in each part, patients can enter an OLE.</p>	<p><u>Part 2 starting dose</u></p> <p>Infants >1 month and <3 months at enrollment: 0.04 mg/kg</p> <p>Infants ≥3 to <5 months: 0.08 mg/kg</p> <p>Infants ≥ 5 months: 0.2 mg/kg.</p> <p>Subsequent Dosing Adjustment: The dose for all infants <2 years has been adjusted to 0.2 mg/kg. (Of the n = 19 subset of patients enrolled at < 5 months of age, n = 4 received 0.2 mg/kg for at least 7 days while < 5 months of age)</p> <p>Infants ≥2 years: 0.25 mg/kg.</p>	<p><u>Part 2:</u></p> <p>41 infants</p>	<p><u>Part 2:</u></p> <p>5.2 (2.2 – 6.9) months</p>	<p><u>Part 2:</u></p> <p>F: 53.7% M: 46.3%</p>

The efficacy of EVRYSDI for the treatment of SMA patients with infantile-onset and later-onset SMA was evaluated in 2 pivotal clinical studies, FIREFISH and SUNFISH. The overall findings of these studies support the effectiveness of EVRYSDI for SMA patients.

Infantile-onset SMA

FIREFISH

Study BP39056 (FIREFISH) is an open-label, 2-part study to investigate the efficacy, safety, PK and pharmacodynamics (PD) of EVRYSDI in symptomatic Type 1 SMA patients (all patients had genetically confirmed disease with 2 copies of the *SMN2* gene). Part 1 of FIREFISH was designed as the dose-finding part of the study. The confirmatory Part 2 of the FIREFISH study assessed the efficacy of EVRYSDI at the therapeutic dose selected based on the results from Part 1 (see [4 DOSAGE AND ADMINISTRATION](#), [4.2 Recommended Dose and Dosage Adjustment](#)). Patients from Part 1 did not take part in Part 2.

In Parts 1 and 2, the key efficacy endpoint was 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 – Third Edition (BSID-III) gross motor scale, after 12 months treatment with EVRYSDI.

FIREFISH Part 2

In FIREFISH Part 2, 41 patients with Type 1 SMA were enrolled. The median age of onset of clinical signs and symptoms of Type 1 SMA was 1.5 months (range: 1.0-3.0 months), 54% were female, 54% Caucasian and 34% Asian. The median age at enrollment was 5.3 months (range: 2.2-6.9 months) and the median time between onset of symptoms and first dose was 3.4 months (range: 1.0-6.0 months). At baseline, the median CHOP-INTEND score was 22.0 points (range: 8.0-37.0) and the median HINE-2 score was 1.0 (range: 0.0-5.0).

Later-Onset SMA

Study BP39055 (SUNFISH), is a 2-part, multicenter trial to investigate the efficacy, safety, pharmacokinetics (PK) and pharmacodynamics (PD) of EVRYSDI in SMA Type 2 or Type 3 patients between 2-25 years of age. Part 1 was the exploratory dose-finding portion and Part 2 was the randomized double-blind placebo-controlled confirmatory portion. Patients from Part 1 did not take part in Part 2.

The primary endpoint was the change from baseline score at month 12 on the Motor Function Measure-32 (MFM32). The MFM32 has the ability to assess a wide range of motor function across a broad range of SMA patients. 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. The MFM32 measures motor function abilities which relate to important daily functions. Small changes in motor function can result in meaningful gain or loss of daily function(s).

SUNFISH Part 2

Part 2 is the randomized, double-blinded, placebo-controlled portion of the SUNFISH study in 180 non-ambulant patients with Type 2 (71%) or Type 3 (29%) SMA. Patients were randomized with 2:1 ratio to receive either EVRYSDI at the therapeutic dose (see [4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment](#)) or placebo. Randomization was stratified by age group (2 to 5, 6 to 11, 12 to 17, 18 to 25 years old).

The median age of patients at the start of treatment was 9.0 years old (range 2-25 years old), the median time between onset of initial SMA symptoms to first treatment was 102.6 (1 - 275) months. Of the 180 patients included in the trial, 51% were female, 67% were Caucasian and 19% were Asian. At baseline, 67% of patients had scoliosis (32% of them with severe scoliosis). Patients had a mean baseline MFM32 score of 46.1 and Revised Upper Limb Module (RULM) score of 20.1. The overall baseline demographic characteristics were well balanced between EVRYSDI and placebo groups with the exception of an imbalance of patients with scoliosis (63.3% of patients in the EVRYSDI arm and 73.3% of patients in the placebo control).

14.5 Study Results

Infantile-onset SMA

FIREFISH Part 2

The primary endpoint, shown in Table 9, was the proportion of patients with the ability to sit without support for at least 5 seconds after 12 months of treatment (BSID-III gross motor scale, Item 22). Key secondary endpoints, at 12 or 24 months of treatment, are also shown.

The efficacy endpoints of EVRYSDI-treated patients were compared to similar cohorts of untreated patients with infantile-onset SMA from natural history (defined as performance criteria) as shown in Table 9.

Table 9 Summary of Key Efficacy Results in Patients with Infantile-Onset SMA at Month 12 and Month 24 of Treatment (FIREFISH Part 2)

Efficacy Endpoints	Proportion of Patients N = 41 (90% CI)
Primary Endpoint at 12 months	
BSID-III: sitting without support for at least 5 seconds p-value based on performance criterion of 5% ^a	29.3% (17.8%, 43.1%) <0.0001
Secondary Endpoints at 12 months	
CHOP-INTEND: score of 40 or higher p-value based on performance criterion of 17% ^a	56.1% (42.1%, 69.4%) <0.0001
CHOP-INTEND: increase of ≥4 points from baseline p-value based on performance criterion of 17% ^a	90.2% (79.1%, 96.6%) <0.0001
HINE-2: motor milestone responders ^b p-value based on performance criterion of 12% ^a	78.0% (64.8%, 88.0%) <0.0001
Event-Free Survival ^c p-value based on performance criterion of 42% ^a	85.4% (73.4%, 92.2%) <0.0001
Secondary Endpoint at 24 months	
BSID-III: sitting without support for at least 30 seconds p-value based on performance criterion of 5% ^a	43.9% (30.6%, 57.9%) <0.0001

CHOP-INTEND=Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2=Module 2 of the Hammersmith Infant Neurological Examination.

- ^a p-values for survival and event-free survival are based on a Z-test; p-values for all other endpoints (BSID-III, CHOP-INTEND, HINE-2) are based on an exact binomial test. Survival proportions estimated using Kaplan-Meier methodology.
- ^b According to HINE-2: ≥2 point increase [or maximal score] in ability to kick, OR ≥1 point increase in the motor milestones of head control, rolling, sitting, crawling, standing or walking, AND improvement in more categories of motor milestones than worsening is defined as a responder for this analysis.
- ^c An event is meeting the endpoint of permanent ventilation defined as tracheostomy or ≥16 hours of non-invasive ventilation per day or intubation for > 21 consecutive days in the absence of, or following the resolution of, an acute reversible event. Three patients met the endpoint of permanent ventilation before Month 12. (All 3 patients achieved an increase of at least 4 points in their CHOP-INTEND score from baseline). By Month 24 one additional patient met the endpoint of permanent ventilation.

These results (Table 9) indicate a clinically meaningful deviation from the natural history of untreated infantile-onset SMA. Untreated patients with infantile-onset SMA would never be able to sit without support, and only 25% would be expected to survive without permanent ventilation beyond 14 months of age. In addition, after 24 months of treatment with EVRYSDI, 93% of patients remained alive, unchanged from Month 12. There were no data to suggest loss of efficacy at Month 24 compared to Month 12. For two additional key secondary outcomes at Month 24 (proportion of infants “standing alone” and proportion “walking alone” [BSID-III gross motor scale, Items 40 and 42, respectively]), the responder rate was 0%, which is not different than the natural history.

FIREFISH Part 1

The efficacy of EVRYSDI in Type 1 SMA patients is also supported by results from FIREFISH Part 1. For the 21 patients from Part 1, the baseline characteristics were consistent with symptomatic patients with Type 1 SMA. The median age at enrollment was 6.7 months (range: 3.3-6.9 months) and the median time between onset of symptoms and first dose was 4.0 months (range: 2.0-5.8 months). A total of 17 patients received 0.2 mg/kg once daily (dose selected for Part 2) during their first 12 months of treatment, with the majority starting that dose after 5 months of age.

After 12 months of treatment, 41% (7/17) of patients were able to sit independently for at least 5 seconds (BSID-III, Item 22). After 18 months of treatment, 88% (15/17) of patients were alive and event-free (without permanent ventilation). These results in survival and motor milestone development were consistent with FIREFISH Part 2.

Later-Onset SMA

SUNFISH Part 2

The primary analysis for SUNFISH Part 2, the change from baseline in MFM32 total score at Month 12 showed a clinically meaningful and statistically significant difference between patients treated with EVRYSDI and placebo. The results of the primary analysis and key secondary endpoints are shown in Table 10, Figure 1.

Table 10 Summary of Efficacy in Patients with Later-Onset SMA at Month 12 of Treatment (SUNFISH Part 2)

Endpoint	EVRYSDI (N = 120)	Placebo (N = 60)
Primary Endpoint:		
Change from baseline in MFM32 total score ¹ at Month 12 LS Mean (95%, CI)	1.36 (0.61, 2.11)	-0.19 (-1.22, 0.84)
Difference from Placebo Estimate (95% CI) p-value ²	1.55 (0.30, 2.81) 0.0156	
Secondary Endpoints:		
Proportion of patients with a change from baseline in MFM32 total score ¹ of 3 or more at Month 12 (95% CI)	38.3% (28.9, 47.6)	23.7% (12.0, 35.4)
Odds ratio for overall response (95% CI) Adjusted ⁴ (unadjusted) p-value ^{3,4}	2.35 (1.01, 5.44) 0.0469 (0.0469)	
Change from baseline in RULM total score ⁵ at Month 12 LS Mean (95% CI)	1.61 (1.00, 2.22)	0.02 (-0.83, 0.87)
Difference from Placebo Estimate (95% CI) adjusted ⁴ (unadjusted) p-value ^{2,4}	1.59 (0.55, 2.62) 0.0469 (0.0028)	

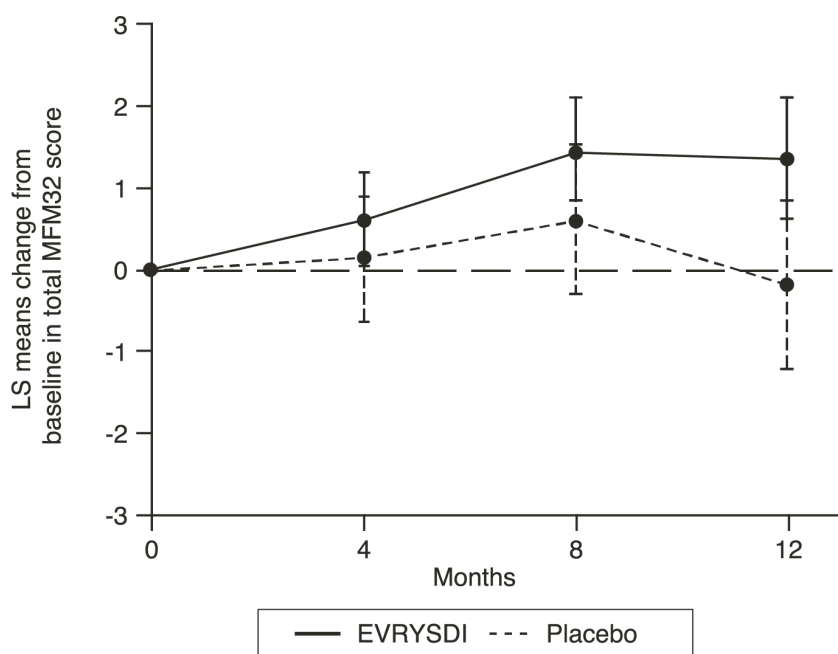
LS=least squares

1. Based on the missing data rule for MFM32, 6 patients were excluded from the analysis (EVRYSDI n=115; placebo control n=59)
2. Data analyzed using a mixed model repeated measure with baseline total score, treatment, visit, age group, treatment-by-visit and baseline-by-visit.
3. Data analyzed using logistic regression with baseline total score, treatment and age group.
4. The adjusted p-value was obtained for the endpoints included in the hierarchical testing and was derived based on all the p-values from endpoints in order of the hierarchy up to the current endpoint. Unadjusted p-value was tested at the 5% significance level.
5. Based on the missing data rule for RULM, 3 patients were excluded from the analysis (EVRYSDI n=119; placebo control n=58)

When compared to placebo, patients treated with EVRYSDI compared to placebo demonstrated significant improvement in motor function assessed by MFM32 (1.55 point mean difference; p = 0.0156) after 12 months of treatment. Consistent improvement compared to baseline MFM32 was observed in both Type 2 and 3 SMA patients (1.54 points [95% CI: 0.06, 3.02]; 1.49 points [95% CI: -0.94, 3.93] respectively) treated with EVRYSDI compared to placebo control.

The study also met a secondary independent motor function outcome, RULM. On the RULM, statistically significant and clinically meaningful improvements in motor function were observed after 12 months of treatment compared to baseline.

Figure 1 Mean Change from Baseline in Total MFM32 Score Over 12 months in SUNFISH Part 2¹



¹The least squares (LS) mean difference for change from baseline in MFM32 score [95% CI]

SUNFISH Part 1

The efficacy of EVRYSDI in later-onset SMA patients was also supported by results from Part 1, the dose-finding part of SUNFISH. In Part 1, 51 patients with Type 2 and 3 SMA (including 7 ambulatory patients) between 2 to 25 years old were enrolled. After 1 year of treatment there was a clinically meaningful improvement in motor function as measured by MFM32 with a mean change from baseline of 2.7 points (95% CI: 1.5, 3.8). The improvement in MFM32 was maintained up to 2 years on EVRYSDI treatment (mean change of 2.7 points [95% CI: 1.2, 4.2]).

15 MICROBIOLOGY

Not applicable.

16 NON-CLINICAL TOXICOLOGY

Safety Pharmacology

In vitro and *in vivo* safety pharmacology studies in rats and monkeys have shown that risdiplam does not display any adverse effects on vital organ functions in the cardiovascular, central nervous or respiratory systems. A clinical trial to characterize the risk of QTc prolongation associated with the oral administration of risdiplam is ongoing.

General Toxicology

Calculation of safety margins was based on mean exposure at the NOAEL of individual monkeys or composite means from rodents, compared to the expected range of exposure (from the therapeutic AUC range of 1060 to 3800 ng·h/mL see 10.3 Pharmacokinetics). It is considered that an arithmetic mean AUC would not accurately reflect the range of patient exposure achieved or associated safety margins, as the dosing regimen is adjusted according to age and weight.

The repeat-dose toxicology program was conducted to assess the safety profile of risdiplam in juvenile and adult rats and monkeys. In all studies, risdiplam was administered by oral gavage in a solution similar to the clinical formulation. Findings of toxicological significance for risdiplam with daily oral dosing were primarily observed in organs with rapid cell turnover in mice, rats and monkeys with onset of less than 14 days of treatment, they were reversible or partially reversible in nature (depending on the chosen reversibility period and cell turnover in the respective organs), and included:

- Findings in gastrointestinal (GI) epithelia (increased apoptosis/single cell necrosis) were reversible at lower exposure multiples, but associated with mortality in mice and rats (in combination with decreased bone marrow cellularity). The range of exposure between tolerability and lethality was narrow in both species (approximately from 2- to 5-times the expected maximal therapeutic exposure).
- Effects on skin, larynx and eyelid histology were evident in mice, rats and monkeys treated with risdiplam. Adverse epithelial changes including those to the lamina propria (vacuolation) and exocrine pancreas (single cell necrosis) in mouse, rat and/or monkey were noted. Parakeratosis/hyperplasia/degeneration of the skin, tongue and larynx epithelia with associated inflammation were observed in monkeys.
- Chronic treatment of monkeys with risdiplam yielded evidence for an effect on the retina in terms of photoreceptor degeneration starting in the periphery of the retina (see 7 WARNINGS AND PRECAUTIONS, Ophthalmology). Upon cessation of treatment, the effects on the retinogram were partially reversible but the photoreceptor degeneration did not reverse. Multifocal peripheral retina degeneration in the photoreceptor layer with hypertrophic retinal pigment epithelium (RPE) and microcystoid spaces (vacuolation) occurring both peripherally and centrally in the inner retinal layers were present in monkeys. These changes were monitored by spectral domain-optical coherence tomography (sdOCT) from week 20 through to week 38 of treatment and confirmed by histology at the end of 39 weeks of treatment. This was associated with depressed scotopic (rod) B wave and somewhat less affected photopic (cone) B wave in the electroretinogram (ERG). The no observed effect level (NOEL) of this finding with 39 weeks of treatment was 1870/2060 ng·h/mL (AUC₀₋₂₄ in M/F) with effects seen in all treated animals by sdOCT and in histology at an exposure \geq 4880/4850 ng·h/mL (AUC₀₋₂₄ in M/F). Depressed ERG and microcystoid spaces in the inner nuclear layer (INL) were only seen in animals at the high dose with an exposure of 5880/6470 ng·h/mL (AUC₀₋₂₄ in M/F). In the 22-week recovery phase, these changes partially regressed morphologically in sdOCT, and functional parameters in ERG returned to normal in 3/4 animals. Histologically, retinal degeneration with photoreceptor loss and RPE hypertrophy were still present but the vacuolation of the INL had reversed. Some experimental data indicate that the effect may be caused by an impairment of photoreceptor recycling in the retinal pigment epithelium. The effect has a clear NOAEL at the clinical dose used for risdiplam. Effects were seen with exposures slightly greater than the anticipated maximal exposure in humans at the therapeutic dose. No such findings were observed in

albino or pigmented rats when dosed chronically with risdiplam at exposures exceeding those in the monkey.

Decreased epididymal and testicular weight, accompanied by degeneration of the seminiferous epithelium and degeneration/atrophy of seminiferous tubules were observed in juvenile and adult rats, with only partial reversibility. This finding occurred with the lowest tested dose in juvenile rats at 744 ng·h/mL (AUC₀₋₂₄) dosed from PND4 - 31. It was also observed in older rats with longer durations of treatment, and in monkeys at exposures of approximately 6000 ng·h/mL AUC₀₋₂₄. Evidence generated with *SMN2* splice modifiers, showed a specific interaction in the pachytene stage of sperm cell differentiation, with later phases expected to be affected with prolonged exposure. The reversibility of these findings could not be fully assessed in monkeys.

- Hematological findings (red and white cells), without histopathological changes in bone marrow but with either small thymus or decreased lymphoid cellularity in the thymus, were observed in mice, rats and monkeys. In mice, albino and pigmented rats, high doses associated with exposures of $\geq 15,000$ ng·h/mL (AUC₀₋₂₄) led to decreased bone marrow cellularity in some pre-terminal deaths and early sacrifices.

In the acute bone marrow micronucleus test in rats, a reduction of more than 50% in the ratio of polychromatic (young) to normochromatic (adult) erythrocytes, indicative of substantial bone marrow toxicity, was observed at the high dose level with exposure ranging from 9 to 30 times the expected therapeutic range in humans. Early deaths and sacrifices likely based on hematological effects were seen with chronic treatment of rats over 26 weeks at the same exposure. The NOAEL for hematological effects in rats treated for 26 weeks was attained at exposures 2 to 7 times the range of exposure achieved in humans at the therapeutic dose. Micronucleus induction in bone marrow was observed in several toxicity studies in rats (adult and juvenile animals) with a NOAEL exposure of approximately 0.5 to 2 times the range of exposure in humans at the therapeutic dose.

Carcinogenicity

A carcinogenicity study with risdiplam in *rasH2* transgenic mice did not give any evidence of tumorigenic potential with animals exposed up to 7-fold the exposure in humans at the therapeutic dose.

A 2-year rat carcinogenicity study is ongoing, and together with the results from the mouse study, will provide a fulsome assessment of the tumorigenic potential for risdiplam.

Genotoxicity

Risdiplam was not mutagenic in a bacterial reverse mutation assay. In mammalian cells *in vitro* and in rat bone marrow erythrocytes, risdiplam increased the frequency of micronucleated cells suggesting clastogenic potential. Micronucleus induction in bone marrow was observed in several toxicity studies in rats (adult and juvenile animals). The no observed adverse effect level (NOAEL) across the studies is associated with an exposure comparable to or below the exposure in humans at the therapeutic dose. Data indicated that this effect is indirect and secondary to an interference of risdiplam with the cell cycle of dividing cells. Risdiplam was not associated with DNA strand breakages in an *in vivo* Comet assay.

Reproductive and Developmental Toxicity

In studies in pregnant rats treated with risdiplam, embryofetal toxicity with lower fetal weight and delayed development was evident. The NOAEL exposure for this effect was approximately 1 to 4 times the exposure levels reached at the therapeutic range of exposure of risdiplam in patients. In studies with pregnant rabbits, embryofetal deaths and dysmorphogenic effects were observed at exposures also associated with maternal toxicity. These consisted of four fetuses (4%) from 4 litters (22%) with hydrocephaly. The maternal exposure at the NOAEL was 2 to 7 times the exposure levels reached at the therapeutic range of exposure of risdiplam in patients.

In a pre- and post-natal development study with pregnant rats treated daily with risdiplam, risdiplam caused a slight delay in gestation length. No adverse effects were recorded on the survival, growth, or behavioral performance of the offspring. Delayed sexual maturation (vaginal opening) and impaired reproductive potential (reduced corpora lutea, implantation sites and live embryos) were noted in offspring from highest dose group. The maternal plasma exposure levels were 0.5 to 1.8 times the therapeutic range of exposure in patients. There were no effects on female germ cells, as assessed by primordial follicle counts and ovarian histopathology.

Studies in pregnant and lactating rats showed that risdiplam crosses the placenta barrier and is excreted into milk (the milk to plasma ratio was > 3 for at least 24 hours following administration of risdiplam).

Impairment of Fertility

Treatment with risdiplam has been associated with male germ cell arrest in rats and monkeys. These effects led to degenerated spermatocytes, degeneration/necrosis of the seminiferous epithelium, and oligo/azospermia in the epididymis. Further, decreased sperm concentrations and motility associated with an increased number of spermatozoa morphology abnormalities were observed. In young rats, effects were seen at exposure levels 0.4 to 1.9 times the therapeutic range of exposure of risdiplam in patients. However, there was no impairment on male fertility seen in a respective study (13-week study with juvenile Wistar Hannover rats). Sperm cell effects of risdiplam are likely related to an interference of risdiplam with the cell cycle of dividing cells, and are stage specific, and are expected to be reversible. No effects were seen on female reproductive organs in rats and monkeys after treatment with risdiplam.

Juvenile animal studies

Risdiplam was studied for toxicity with chronic administration in rats and monkeys including juvenile animal studies. Studies in juvenile animals did not indicate any specific effect of treatment with risdiplam on developing organ systems, but was associated with delayed growth (body weight and long bones), as well as delayed sexual maturity in males (pre-weaning). In terms of toxicity seen after treatment with risdiplam in various organ systems with high cell turnover (skin, GI-tract, bone marrow), animal studies do not indicate any differences in sensitivity between juvenile, adolescent and adult animals, i.e. the respective NOAELs were comparable with those seen in adult animals. At comparable exposures, incidences and severity of the adverse effects were not more pronounced in juvenile animals than in adult animals.

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Pr **EVERYSDI**[®]
Risdiplam Powder for Oral Solution

Read this carefully before you start taking **EVERYSDI** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **EVERYSDI**.

What is EVRYSDI used for?

- EVRYSDI is a medicine used to treat spinal muscular atrophy (SMA), which is a condition that affects the nervous system.
- EVRYSDI is for use in children 2 months of age and older and in adults.

How does EVRYSDI work?

EVRYSDI works by helping the body make more of a protein called “SMN protein”. EVRYSDI increases the amount of SMN protein in the body, which helps to treat SMA.

What are the ingredients in EVRYSDI?

Medicinal ingredients: risdiplam

Non-medicinal ingredients: ascorbic acid, disodium edetate dihydrate, isomalt, macrogol/polyethylene glycol 6000, mannitol, sodium benzoate, strawberry flavor, sucralose, tartaric acid.

EVRYSDI comes in the following dosage forms:

Powder for oral solution, 60 mg/bottle (0.75 mg/mL when reconstituted). The total volume when reconstituted is 80 mL.

Do not use EVRYSDI if:

- You are allergic to risdiplam or any of the other ingredients in EVRYSDI or components of the container (see “**What are the ingredients in EVRYSDI?**” for a list of ingredients).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take EVRYSDI. Talk about any health conditions or problems you may have, including if you:

- are pregnant, think you may be pregnant or plan to become pregnant
- are breastfeeding or plan to breastfeed
- have a fructose/sugar intolerance, EVRYSDI contains isomalt and mannitol

Other warnings you should know about:

Pregnancy: EVRYSDI may harm your unborn baby. Your doctor may require you to do a pregnancy test before you start treatment with EVRYSDI to make sure you are not pregnant. You must use a reliable form of birth control during treatment. Do not become pregnant during treatment or for at least 1 month after you stop taking EVRYSDI. If you do become pregnant, tell your doctor right away.

Use in Men: EVRYSDI may impact male fertility during treatment, but is reversible once you stop treatment. If your partner can get pregnant, make sure to use condoms during sex when you are taking EVRYSDI. Use condoms for at least 4 months after you finish treatment. Do not donate sperm during treatment and for at least 4 months after your last dose of EVRYSDI.

Talk to your healthcare professional if you have interest in starting a family.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with EVRYSDI:

- nusinersen, another drug used to treat SMA

How to take EVRYSDI:

- Carefully read and follow the “Instructions for Use” before you take or give EVRYSDI
- Always take or give EVRYSDI exactly as your healthcare professional tells you to, if you are unsure, talk to your healthcare professional
- Do not stop taking EVRYSDI or change the dose unless your doctor tells you to
- Only use the oral syringes provided as they are designed to protect the medication from light
- EVRYSDI can be taken with or without food
- Do not mix EVRYSDI with formula or milk
- Take or give EVRYSDI at the same time each day

Usual dose:

- **Adolescents and adults:** The daily dose of EVRYSDI is 5 mg (6.6 mL of the 0.75 mg/mL oral solution).
- **Infants and children:** Your doctor will determine the daily dose of EVRYSDI based on your child’s age and weight.

Drink or give your child a tablespoon (15 mL) of water right after taking EVRYSDI.

If you or your child do not swallow the full dose, or vomit after taking a dose of EVRYSDI, do not take or give an extra dose. Take the next dose at the usual time the next day.

Overdose:

If you think you, or a person you are caring for, have taken too much EVRYSDI, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- If the missed dose is within 6 hours of when you normally take or give EVRYSDI, take or give the missed dose as soon as you remember.
- If the missed dose is over 6 hours from when you normally take or give EVRYSDI, skip the missed dose and then take or give the next dose at the usual time.

Do not take or give a double dose to make up for a forgotten dose.

What are possible side effects from using EVRYSDI?

These are not all the possible side effects you or your child may feel when taking EVRYSDI. If you or your child experience any side effects not listed here, contact your healthcare professional.

- diarrhea
- constipation
- vomiting
- fever
- urinary tract infection
- rash
- canker or ulcer sores in the mouth
- joint pain

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Cutaneous vasculitis [inflamed blood vessels in the skin. Symptoms include a red or purple rash (from small dots to larger raised bruises), that may be itchy or painful, and is usually on the lower half of the body. It can sometimes also affect other places in the body such as the joints or kidneys]		✓	

If you or your child have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store the oral solution in the refrigerator at 2°C to 8°C. Do not freeze.
- Keep the oral solution in the original amber bottle in an upright position.
- Take EVRYSDI immediately after it is drawn up into the oral syringe. If it is not taken within 5 minutes, discard the dose and prepare a new one.
- Do not store the EVRYSDI solution in the syringe.
- Wash the syringes per instructions after use. Do not throw the oral syringe away.
- The oral solution can be used for 64 days after reconstitution by your healthcare professional. Discard the medicine after the “DISCARD AFTER” date written on the bottle label.

Keep out of reach and sight of children.

If you want more information about EVRYSDI:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>); the manufacturer’s website www.rochecanada.com, or by calling 1-888-762-4388.

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INSTRUCTIONS FOR RECONSTITUTION

EVRYSDI®

risdiplam powder for oral solution

(FOR HEALTHCARE PROFESSIONALS ONLY)

Each EVRYSDI carton contains (See figure A):

1. 1 Cap
 2. 1 EVRYSDI bottle
 3. 2 Re-useable oral syringes 12 mL (in pouches)
 4. 2 Re-useable oral syringes 6 mL (in pouches)
 5. 1 Press-in bottle adapter
- 1 Booklet containing the Patient Medication Information Leaflet (not shown), Instructions for Reconstitution (not shown), and Instructions for Use (not shown)

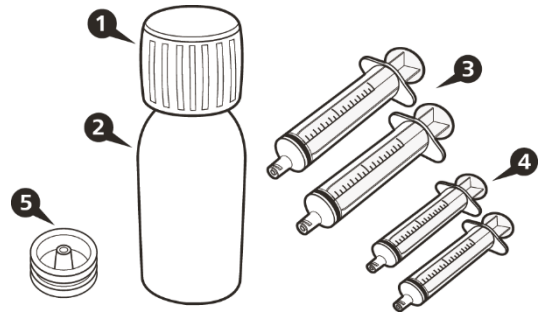


Figure A

Important information about EVRYSDI

- **Avoid inhaling** EVRYSDI powder.
- **Use gloves.**
- **Do not** use if the powder expiry date has passed. The powder expiration date is printed on the bottle label.
- **Do not** dispense the reconstituted solution if the solution's Discard After date exceeds the original powder expiration date.
- **Avoid getting contact** with the medicine on your skin. If the medicine gets on your skin, wash the area with soap and water.
- **Do not** use the medicine if any of the supplies are damaged or missing.
- Use Purified Water or Water for Injection (WFI) to reconstitute the medicine.
- Do not add oral syringes other than the ones provided in the carton.

How to store EVRYSDI

- Store the powder (unreconstituted medicine) at room temperature (15 – 25°C) and keep it in the carton.
- Store the solution (reconstituted medicine) in a refrigerator between 2°C to 8°C.
- Keep the oral solution in the original bottle and always keep the bottle in an upright position with the cap tightly closed.

Reconstitution

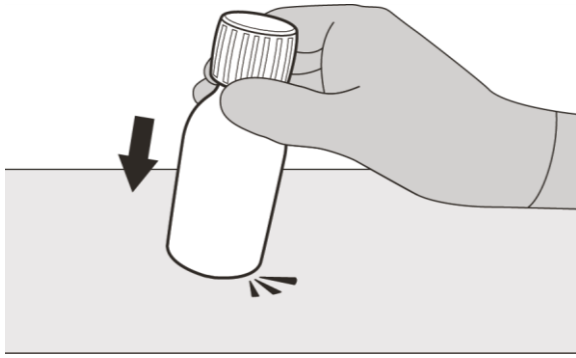


Figure B

Step 1

Gently tap the bottom of the bottle to loosen the powder (See Figure B).

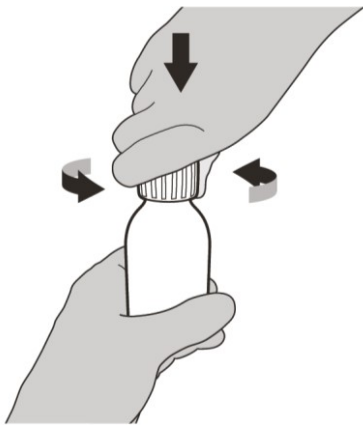


Figure C

Step 2

Remove the cap by pushing it down and then twisting to the left (counter-clockwise) (See Figure C). Do not throw away the cap.



Figure D

Step 3

Carefully pour 79 mL of Purified Water or Water for Injection (WFI) into the medicine bottle (See Figure D).

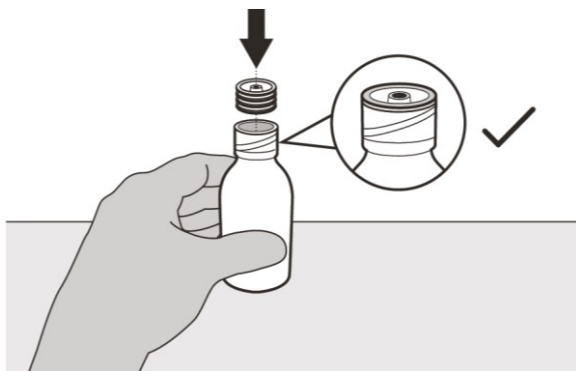


Figure E

Step 4

Hold the medicine bottle on a table with one hand.

Insert the press-in bottle adapter into the opening by pushing it down with the other hand. Ensure it is completely pressed against the bottle lip (See Figure E).

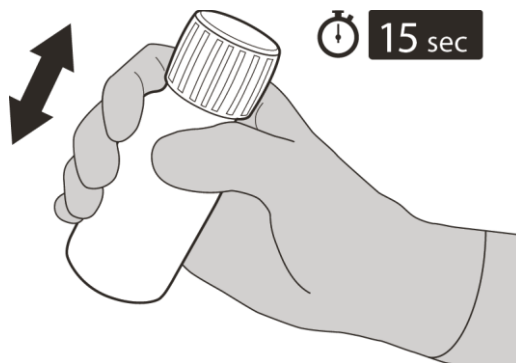


Figure F

Step 5

Put the cap back on the bottle. Turn the cap to the right (clockwise) to close the bottle.

Ensure it is completely closed and then shake well for 15 seconds (See Figure F).

Wait for 10 minutes. You should have obtained a **clear solution**.

If not, shake well again for another 15 seconds.

Step 6

Calculate the Discard After date as **64 days** after reconstitution (Note: the day of reconstitution is counted as day 0. For example, if reconstitution is on the 1st of April, the Discard After date will be the 4th of June).

Write the Discard After date of the solution on the bottle label (See Figure G)

Put the bottle back in its original carton, with syringes (in pouches), booklet. Store the carton into the refrigerator.



Figure G

EVRYSDI® (risdiplam powder for oral solution)

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Instructions for Reconstitution version date: May-19-2021

NEOCONNECT AT HOME ORAL/ENTERAL SYRINGE WITH ENFIT CONNECTOR, REUSABLE (NEO6-BA & NEO12-BA) are manufactured by NeoMed, Inc., Woodstock, GA 30188, USA Press-in bottle adapter is manufactured by Miktell Ltd. High Wycombe, HP11 1JU, UK

INSTRUCTIONS FOR USE

EVRYSDI®

risdiplam powder for oral solution

(FOR PATIENT USE)

Be sure to read and understand this **Instructions for Use** before you start using EVRYSDI for information on how to prepare and give EVRYSDI through an oral syringe, gastrostomy tube (G-tube), or nasogastric tube (NG-tube).

If you have any questions about how to use EVRYSDI, contact your healthcare provider.

EVRYSDI should come as a liquid in a bottle when you receive it. **Do not** use if the medicine in the bottle is a powder and contact your healthcare provider.

Each EVRYSDI carton contains (See figure A):

- 1.** 1 EVRYSDI bottle with bottle adapter and cap
- 2.** 2 Re-useable oral syringes 6 mL (in pouches)
- 3.** 2 Re-useable oral syringes 12 mL (in pouches)
- 4.** 1 Booklet containing the Patient Medication Information (not shown), Instructions for Reconstitution (not shown) and Instructions for Use (not shown)

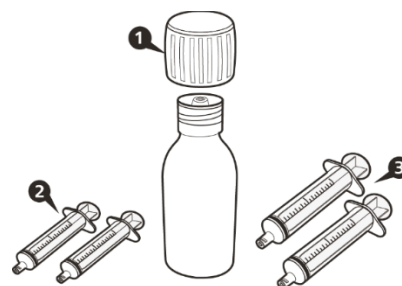


Figure A

How to store EVRYSDI

Please see 'Storage' of the Patient Medication Information for full information.

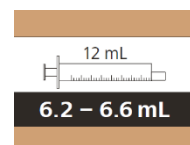
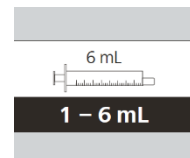
Important information about EVRYSDI

- Ask your healthcare provider to show you the correct syringe you should use and how to measure your prescribed daily dose.
- Always use the re-usable oral syringes provided in the carton to measure your prescribed daily dose. The oral syringe protects the medicine from light.
- Two oral syringes of each size are provided in case one gets lost or damaged. Contact your healthcare provider if both oral syringes are lost or damaged. They will advise you on how to continue to take your medicine.
- See “**How to select the correct oral syringe to use for your prescribed dose of EVRYSDI**” for the correct oral syringe you should use. Ask your pharmacist if you have questions on how to select the right oral syringe.
- If the bottle adapter is not in the bottle, **do not** use EVRYSDI and then contact your pharmacist.
- **Do not** use EVRYSDI after the **Discard after** date written on the bottle label. Ask your pharmacist for the **Discard after** date if it is not written on the bottle label.
- **Do not** mix EVRYSDI into food or liquids.
- **Do not** use EVRYSDI if the bottle or oral syringes are damaged.
- **Avoid** getting EVRYSDI on your or your child’s skin. If EVRYSDI gets on your or your child’s skin, wash the area with soap and water.
- If you spill EVRYSDI, dry the area with a dry paper towel and clean with soap and water. Throw away the paper towel in the waste and wash your hands well with soap and water.
- If there is not enough EVRYSDI left in the bottle for the prescribed dose, discard the bottle with remaining EVRYSDI and used oral syringes according to your local requirements; use a new bottle of EVRYSDI to obtain the prescribed dose. **Do not mix** EVRYSDI from the new bottle with the bottle you are currently using.

A) Preparing and withdrawing your dose

How to select the correct oral syringe to use for your prescribed dose of EVRYSDI

- If the prescribed dose of EVRYSDI is between 1 mL and 6 mL, use a 6 mL oral syringe (grey label).
- If the prescribed daily dose of EVRYSDI is 6.2 mL or higher, use a 12 mL oral syringe (brown label).



How to prepare your dose of EVRYSDI

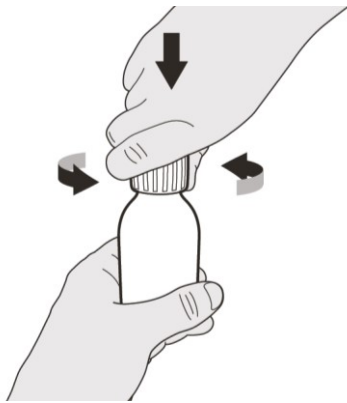


Figure B

Step A1

Remove the cap by pushing it down and then twisting the cap to the left (counter-clockwise) (See Figure B). Do not throw away the cap.

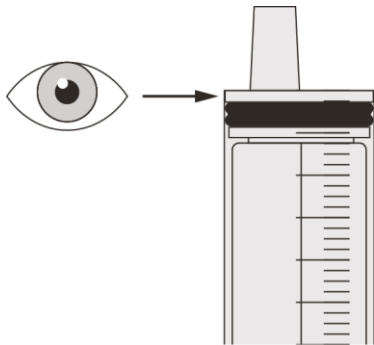


Figure C

Step A2

Push the plunger of the oral syringe all the way down to remove any air in the oral syringe (See Figure C).

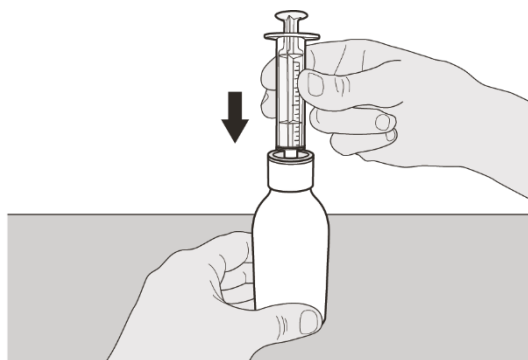


Figure D

Step A3

Keeping the bottle in an upright position, insert the syringe tip into the bottle adapter (See Figure D).

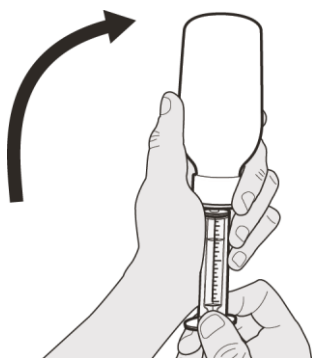


Figure E

Step A4

Carefully turn the bottle upside down with the syringe tip firmly inserted into the bottle adapter (See Figure E).

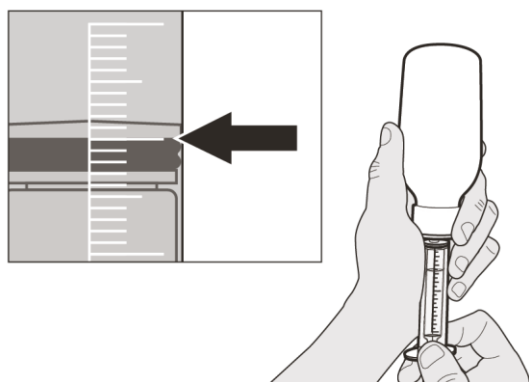


Figure F

Step A5

Slowly pull back on the plunger to withdraw your prescribed dose of EVRYSDI. The top of the black plunger stopper must line up with the mL marking on the oral syringe for your prescribed daily dose (See Figure F).

After the correct dose is withdrawn, **hold the plunger in place to keep the plunger from moving.**

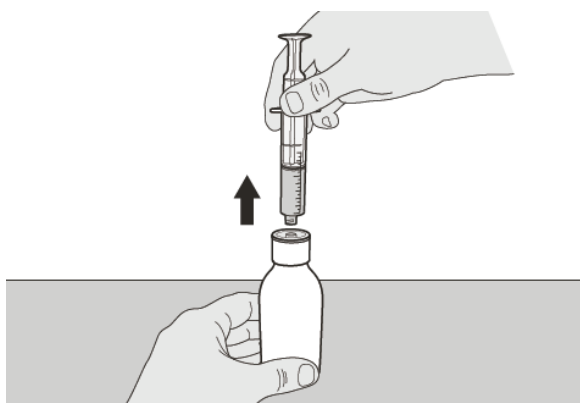


Figure G

Step A6

Continue to hold the plunger in place to keep the plunger from moving. Leave the oral syringe in the bottle adapter and turn the bottle to an upright position. Place the bottle onto a flat surface. Remove the oral syringe from the bottle adapter by gently pulling straight up on the oral syringe (See Figure G).

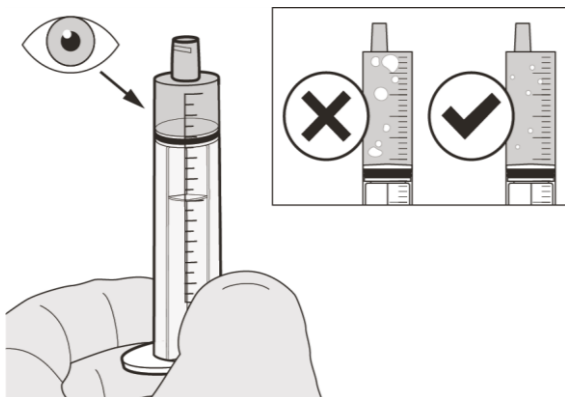


Figure H

Step A7

Hold the oral syringe with the syringe tip pointing up. Check the medicine in the oral syringe. **If** there are large air bubbles in the oral syringe (See Figure H) **or** if you have drawn up the wrong dose of EVRYSDI, insert the syringe tip firmly into the bottle adapter. Push the plunger all the way down so that the medicine flows back into the bottle and repeat Steps A4 through A7.

Take or give EVRYSDI immediately after it is drawn up into the oral syringe.

If it is not taken **within 5 minutes**, discard from oral syringe and prepare a new dose.

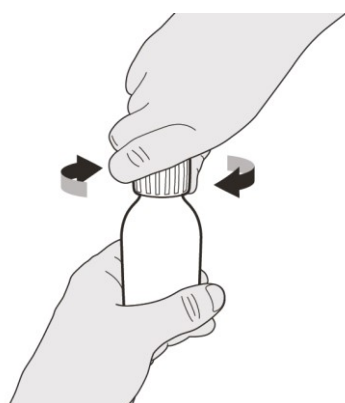


Figure I

Step A8

Put the cap back on the bottle. Turn the cap to the right (clockwise) to tightly close the bottle (See Figure I). Do not remove the bottle adapter from the bottle.

If you are taking or giving the dose of EVRYSDI by mouth, follow the instructions in **“B) How to take a dose of EVRYSDI by mouth”**.

If you are giving the dose of EVRYSDI through a gastrostomy tube, follow the instructions in **“C) How to give a dose of EVRYSDI through a gastrostomy tube”**.

If you are giving the dose of EVRYSDI through a nasogastric tube, follow the instructions in **“D) How to give a dose of EVRYSDI through a nasogastric tube”**.

B) How to take a dose of EVRYSDI by mouth

Sit upright or place your child in an upright position when taking or giving a dose of EVRYSDI by mouth.



Figure J

Step B1

Place the oral syringe into the mouth **with the tip along either cheek.**

Slowly push the plunger all the way down to take the full dose of EVRYSDI (See Figure J).

Giving EVRYSDI into the throat or too fast may cause choking.

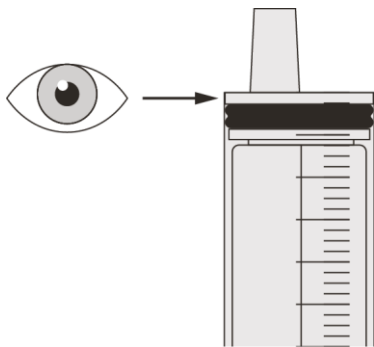


Figure K

Step B2

Check that there is no medicine left in the oral syringe (See Figure K).



Figure L

Step B3

Drink or give your child a tablespoon (15 mL) of water right after taking the prescribed dose of EVRYSDI (See Figure L).

Do not mix EVRYSDI with formula or milk.

Go to Step E for cleaning of the syringe.

C) How to give a dose of EVRYSDI through a gastrostomy tube

If you are giving EVRYSDI through a gastrostomy tube, ask your doctor to show you how to inspect the gastrostomy tube before giving EVRYSDI.

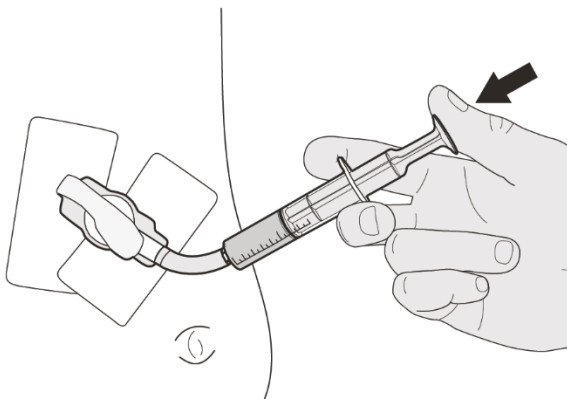


Figure M

Step C1

Place the oral syringe tip into the gastrostomy tube. Slowly push the plunger all the way down to give the full dose of EVRYSDI (See Figure M).

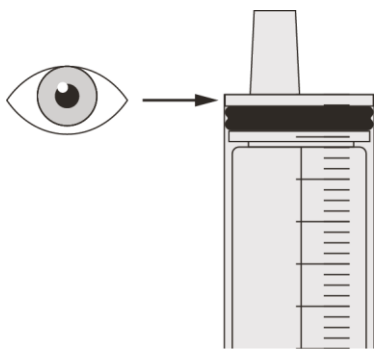


Figure N

Step C2

Check that there is no medicine left in the oral syringe (See Figure N).

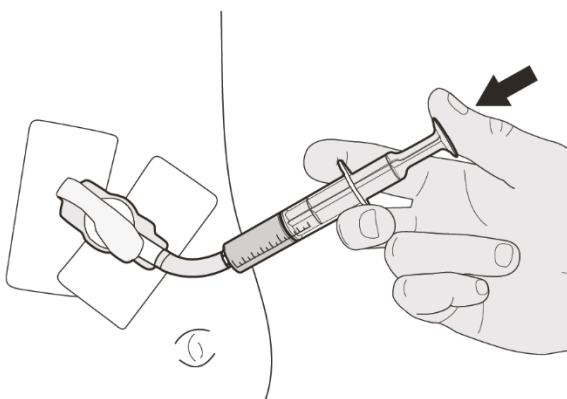


Figure O

Step C3

Flush the gastrostomy tube with 10-20 mL of water right after giving the prescribed dose of EVRYSDI (See Figure O).

Go to Step E for cleaning of the syringe.

D) How to give a dose of EVRYSDI through a nasogastric tube

If you are giving EVRYSDI through a nasogastric tube, ask your doctor to show you how to inspect the nasogastric tube before giving EVRYSDI.

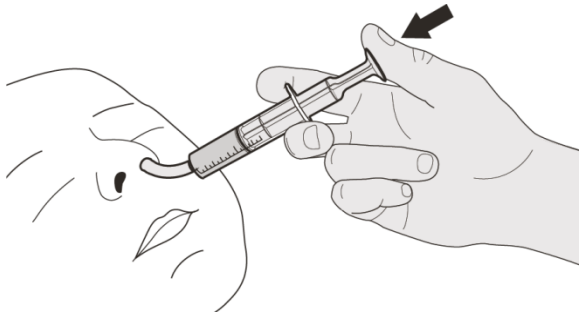


Figure P

Step D1

Place the oral syringe tip into the nasogastric tube. Slowly press the plunger all the way down to give the full dose of EVRYSDI (See Figure P).

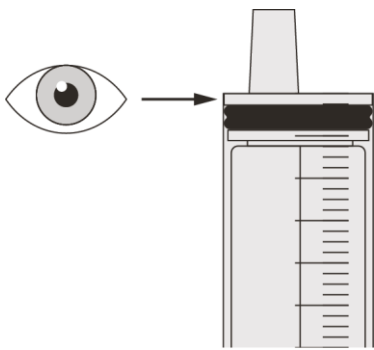


Figure Q

Step D2

Check that there is no medicine left in the oral syringe (See Figure Q).

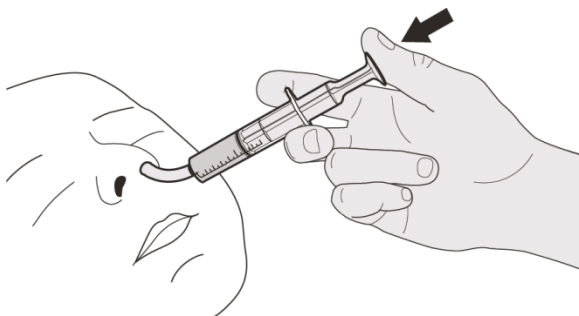


Figure R

Step D3

Flush the nasogastric tube with 10-20 mL of water right after giving the prescribed dose of EVRYSDI (See Figure R).

Go to Step E for cleaning of the syringe.

E) How to clean the oral syringe after use

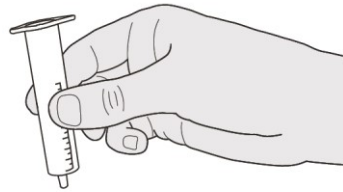
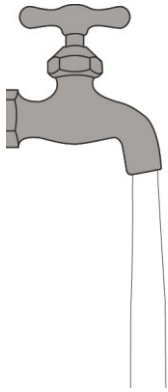


Figure S

Step E1

Remove the plunger from the oral syringe.

Rinse the oral syringe barrel well under clean water (See Figure S).

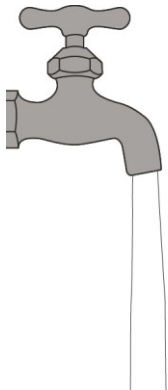


Figure T

Step E2

Rinse the plunger well under clean water (See Figure T).

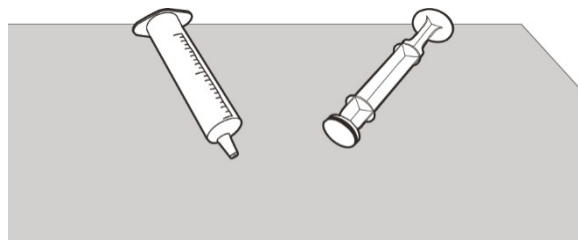


Figure U

Step E3

Check that the oral syringe barrel and plunger are clean.

Place the oral syringe barrel and plunger on a clean surface in a safe place to dry (See Figure U).

Wash your hands.

Once dry, reassemble the plunger into the oral syringe barrel and store the syringe with your medicine.

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Instructions for Use version date: May-19-2021

NEOCONNECT AT HOME ORAL/ENTERAL SYRINGE WITH ENFIT CONNECTOR, REUSABLE

(NEO6-BA & NEO12-BA) are manufactured by NeoMed, Inc., Woodstock, GA 30188, USA

Press-in bottle adapter is manufactured by Miktell Ltd. High Wycombe, HP11 1JU, UK