

# EVERYSDI 0.75mg/mL

Powder for Oral Solution  
Risdiplam

## 1. INDICATIONS AND USAGE

EVERYSDI is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

## 2. DOSAGE AND ADMINISTRATION

### 2.1 DOSING INFORMATION

EVERYSDI is administered orally once daily with or without food. The recommended dosage is determined by age and body weight (see Table 1).

**Table 1 Adult and Pediatric Dosing Regimen by Age and Body Weight**

| Age and Body Weight                               | Recommended Daily Dosage |
|---------------------------------------------------|--------------------------|
| Less than 2 months of age                         | 0.15 mg/kg               |
| 2 months to less than 2 years of age              | 0.2 mg/kg                |
| 2 years of age and older weighing less than 20 kg | 0.25 mg/kg               |
| 2 years of age and older weighing 20 kg or more   | 5 mg                     |

### 2.2 IMPORTANT ADMINISTRATION INSTRUCTIONS

It is recommended that a healthcare provider discuss with the patient or caregiver how to prepare the prescribed daily dose prior to administration of the first dose [see *Instructions for Use*].

EVERYSDI is taken orally once daily with or without food at approximately the same time each day.

In infants who are breastfed, EVERYSDI can be administered before or after breastfeeding. EVERYSDI cannot be mixed with formula or milk.

Instruct patients or caregivers to administer the dose using the reusable oral syringe provided.

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

Instruct patients to drink water after taking EVERYSDI to ensure the drug has been completely swallowed.

If the patient is unable to swallow and has a nasogastric or gastrostomy tube, EVERYSDI can be administered via the tube. The tube should be flushed with water after delivering EVERYSDI [see *Instructions for Use*].

### 2.3 MISSED DOSE

If a dose of EVERYSDI is missed, EVERYSDI 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 day.

If a dose is not fully swallowed or vomiting occurs after taking a dose of EVERYSDI, 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.

## **2.4 PREPARATION OF ORAL SOLUTION BY HEALTHCARE PROFESSIONALS**

EVERYSDI powder must be constituted to the oral solution by a healthcare professional prior to dispensing to the patient.

### Preparation of the EVERYSDI Oral Solution 0.75 mg/mL

The EVERYSDI “Instructions for Constitution” booklet contains more detailed instructions on the preparation of the oral solution [see *Instructions for Constitution*].

Caution should be exercised when handling EVERYSDI powder for oral solution. Avoid inhalation and direct contact with skin or mucous membranes with the dry powder and the constituted solution. If such contact occurs, wash thoroughly with soap and water; rinse eyes with water. Wear disposable gloves during the preparation and cleanup procedure.

1. Gently tap the bottom of the closed glass bottle to loosen the powder.
2. Remove the cap. Do not throw away the cap.
3. Carefully pour 79 mL of purified water into the EVERYSDI bottle to yield the 0.75 mg/mL oral solution. Do not mix EVERYSDI with formula or milk.
4. Insert the press-in bottle adapter into the bottle opening by pushing it down against the bottle lip. Ensure it is completely pressed against the bottle lip.
5. Re-cap the bottle tightly and shake well for 15 seconds. Wait for 10 minutes. You should have obtained a clear solution. If not, shake well again for another 15 seconds or until you have obtained a clear solution.
6. Write the date of expiration of the constituted oral solution (calculated as 64 days after constitution) and the lot number on the bottle label. Peel off the part of the bottle label that has the expiration date of the powder.
7. Put the bottle back in its original carton.
8. Select the appropriate oral syringes (1 mL, 6 mL, or 12 mL) based on the patient’s dosage and remove the other oral syringes from the carton.
9. Dispense with the “Instructions for Use” and package insert. Alert patients to read the important handling information described in the Instructions for Use.

### Storage

Keep the constituted oral solution of EVERYSDI in the original amber bottle to protect from light. Store in a refrigerator at 2°C to 8°C (36°F to 46°F). Do not freeze. Discard any unused portion 64 days after constitution. Keep the bottle in an upright position with the cap tightly closed. If refrigeration is not available, EVERYSDI can be kept at room temperature up to 40°C (up to 104°F) for a combined total of 5 days. EVERYSDI can be removed from, and returned to, a refrigerator. The total combined time out of refrigeration should not exceed 5 days.

## **3. DOSAGE FORMS AND STRENGTHS**

EVERYSDI for oral solution: 60 mg as a light yellow, yellow, greyish yellow, greenish yellow, or light green powder for constitution. Following constitution, the volume of the greenish yellow to yellow solution is 80 mL, providing 60 mg/80 mL (0.75 mg/mL) risdiplam.

## **4. CONTRAINDICATIONS**

EVERYSDI is contraindicated in patients with a known hypersensitivity to risdiplam or any of the excipients.

## **5. WARNINGS AND PRECAUTIONS**

### **5.1.1 GENERAL**

#### **Embryo-fetal Toxicity**

Embryo-fetal toxicity has been observed in animal studies (see section 12 *Nonclinical Toxicology*). Patients of reproductive potential should be informed of the risks and must use highly effective contraception during

treatment and until at least 1 month after the last dose of EVRYSDI in female patients, and 4 months after the last dose of EVRYSDI in male patients. (see section 9 *Use in Specific Populations*).

### Potential Effects on Male Fertility

Due to reversible effects of EVRYSDI 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 EVRYSDI. (see sections 9 *Use in Specific Populations* and 12 *Nonclinical Toxicology; Impairment of Fertility*).

#### 5.1.2 DRUG ABUSE AND DEPENDENCE

EVRYSDI does not have the potential to lead to abuse and dependence.

#### 5.1.3 ABILITY TO DRIVE AND USE MACHINES

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

## 6. ADVERSE REACTIONS

### 6.1 CLINICAL TRIALS EXPERIENCE

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials including patients with infantile-onset SMA, later-onset SMA, and pre-symptomatic SMA, a total of 491 patients (51% female, 74% Caucasian) were exposed to EVRYSDI for up to a median duration of 48.1 months (range: 0.6 to 63.4 months), with 231 patients receiving treatment for more than 24 months. At the time of first EVRYSDI dose, 90 (18%) patients were 18 years and older, 119 (24%) were 12 years to less than 18 years, 189 (39%) were 2 years to less than 12 years, and 67 (14%) 2 months to less than 2 years, and 26 (5%) were less than 2 months.

#### Clinical Trial in Later-Onset SMA

The safety of EVRYSDI for later-onset SMA is based on data from a randomized, double-blinded, placebo-controlled study (Study 2 Part 2) in patients with SMA Type 2 or 3 (n = 180) [see *Clinical Studies (13.2)*]. The patient population in Study 2 Part 2 ranged in age from 2 to 25 years at the time of the first dose.

The most common adverse reactions (reported in at least 10% of patients treated with EVRYSDI and at an incidence greater than on placebo) in Study 2 Part 2 were fever, diarrhea, and rash. Table 2 lists the adverse reactions that occurred in at least 5% of patients treated with EVRYSDI and at an incidence  $\geq$  5% greater than on placebo in Study 2 Part 2.

**Table 2 Adverse Reactions Reported in  $\geq$  5% of Patients Treated with EVRYSDI and with an Incidence  $\geq$  5% Greater Than on Placebo in Study 2 Part 2**

| Adverse Reaction                     | EVRYSDI<br>(N = 120)<br>% | Placebo<br>(N = 60)<br>% |
|--------------------------------------|---------------------------|--------------------------|
| Fever <sup>1</sup>                   | 22                        | 17                       |
| Diarrhea                             | 17                        | 8                        |
| Rash <sup>2</sup>                    | 17                        | 2                        |
| Mouth and aphthous<br>ulcers         | 7                         | 0                        |
| Arthralgia                           | 5                         | 0                        |
| Urinary tract infection <sup>3</sup> | 5                         | 0                        |

<sup>1</sup> Includes pyrexia and hyperpyrexia.

<sup>2</sup> Includes rash, erythema, rash maculo-papular, rash erythematous, rash papular, dermatitis allergic, and folliculitis.

<sup>3</sup> Includes urinary tract infection and cystitis.

### Clinical Trial in Infantile-Onset SMA

The safety of EVRYSDI therapy for infantile-onset SMA is based on data from an open-label study in 62 patients (Study 1) [see *Clinical Studies* (13.1)]. The patient population ranged in age from 2 to 7 months at the time of the first EVRYSDI dose (weight range 4.1 to 10.6 kg).

The most frequent adverse reactions reported in infantile-onset SMA patients treated with EVRYSDI in Study 1 were similar to those observed in later-onset SMA patients in Study 2. Additionally, the following adverse reactions reported in  $\geq 10\%$  of patients were: upper respiratory tract infection (including nasopharyngitis, rhinitis), lower respiratory tract infection (including pneumonia, bronchitis), constipation, vomiting, and cough.

### Clinical Trial in Pre-Symptomatic SMA

The safety of EVRYSDI therapy for pre-symptomatic SMA is based on data from an open-label, single-arm study in 26 patients (Study 3) [see *Clinical Studies* (13.3)]. The patient population ranged in age from 16 to 41 days at the time of the first dose (weight range 3.1 to 5.7 kg). The safety profile of EVRYSDI in pre-symptomatic patients in Study 3 is consistent with the safety profile for symptomatic SMA patients treated with EVRYSDI in clinical trials.

## **7. OVERDOSE**

There is no 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.

## **8. DRUG INTERACTIONS**

### **8.1 EFFECT OF EVRYSDI ON SUBSTRATES OF MULTIDRUG AND TOXIN EXTRUSION (MATE) PROTEIN TRANSPORTERS**

Based on in vitro data, EVRYSDI may increase plasma concentrations of drugs eliminated via MATE1 or MATE2-K [see *Clinical Pharmacology* (11.3)], 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 coadministered drug (based on the labeling of that drug) if needed.

## **9. USE IN SPECIFIC POPULATIONS**

### **9.1 PREGNANCY**

#### Risk Summary

There are no adequate data on the developmental risk associated with the use of EVRYSDI in pregnant women. In animal studies, administration of risdiplam during pregnancy or throughout pregnancy and lactation resulted in adverse effects on development (embryofetal mortality, malformations, decreased fetal body weights, and reproductive impairment in offspring) at or above clinically relevant drug exposures [see *Data*].

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Based on animal data, advise pregnant women of the potential risk to the fetus.

#### Data

##### *Animal Data*

Oral administration of risdiplam (0, 1, 3, or 7.5 mg/kg/day) to pregnant rats throughout organogenesis resulted in decreased fetal body weights and increased incidences of fetal structural variations at the

highest dose tested, which was not associated with maternal toxicity. The no-effect level for adverse effects on embryofetal development (3 mg/kg/day) was associated with maternal plasma exposure (AUC) approximately 2 times that in humans at the maximum recommended human dose (MRHD) of 5 mg.

Oral administration of risdiplam (0, 1, 4, or 12 mg/kg/day) to pregnant rabbits throughout organogenesis resulted in embryofetal mortality, fetal malformations (hydrocephaly), and structural variations at the highest dose tested, which was associated with maternal toxicity. The no-effect dose for adverse effects on embryofetal development (4 mg/kg/day) was associated with maternal plasma exposure (AUC) approximately 4 times that in humans at the MRHD.

When risdiplam (0, 0.75, 1.5, or 3 mg/kg/day) was orally administered to rats throughout pregnancy and lactation, gestation was prolonged in the dams, and delayed sexual maturation (vaginal opening) and impaired reproductive function (decreased numbers of corpora lutea, implantation sites, and live embryos) were observed in female offspring at the highest dose. The no-effect dose for adverse effects on pre- and postnatal development in rats (1.5 mg/kg/day) was associated with maternal plasma exposure (AUC) similar to that in humans at the MRHD.

## **9.2 LACTATION**

### Risk Summary

There are no data on the presence of risdiplam in human milk, the effects on the breastfed infant, or the effects on milk production. Risdiplam was excreted in the milk of lactating rats orally administered risdiplam.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EVRYSDI and any potential adverse effects on the breastfed infant from EVRYSDI or from the underlying maternal condition.

## **9.3 FEMALES AND MALES OF REPRODUCTIVE POTENTIAL**

Studies of risdiplam in juvenile and adult rats and in monkeys demonstrated adverse effects on the reproductive organs, including germ cells, in males at clinically-relevant plasma exposures [see *Use in Specific Populations* (9.4) and *Nonclinical Toxicology* (12.1)].

### Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating EVRYSDI [see *Use in Specific Populations* (9.1)].

### Contraception

EVRYSDI may cause embryofetal harm when administered to a pregnant woman [see *Use in Specific Populations* (9.1)].

### *Female Patients*

Advise female patients of reproductive potential to use effective contraception during treatment with EVRYSDI and for at least 1 month after her last dose.

### Infertility

### *Male Patients*

Male fertility may be compromised by treatment with EVRYSDI [see *Nonclinical Toxicology* (12.1)].

Counsel male patients of reproductive potential receiving EVRYSDI about the potential effects on fertility. Male patients may consider sperm preservation prior to treatment.

## **9.4 PEDIATRIC USE**

The safety and effectiveness of EVRYSDI in pediatric patients (neonates and older) have been established. Use of EVRYSDI for SMA is supported by evidence from adequate and well-controlled studies of EVRYSDI in patients 2 months of age and older with SMA. Use of EVRYSDI for SMA in patients 2 months of age and younger is supported by pharmacokinetic and safety data from pediatric patients 16 days and older, and

pharmacokinetic modeling and simulation to identify the dosing regimen [see *Clinical Pharmacology (11.3) and Clinical Studies (13)*].

### Juvenile Animal Toxicity Data

Oral administration of risdiplam (0, 0.75, 1.5, 2.5 mg/kg/day) to young rats from postnatal day (PND) 4 through PND 31 resulted in decreased growth (body weight, tibia length) and delayed sexual maturation in males at the mid and high dose. The skeletal and body weight deficits persisted after cessation of dosing. Ophthalmic changes consisting of vacuoles in the anterior vitreous were seen at the high dose. Decreases in absolute B lymphocyte counts were observed at all doses after cessation of dosing. Decreases in testis and epididymis weights, which correlated with degeneration of the seminiferous epithelium in the testis, occurred at the mid and high doses; the histopathology findings were reversible, but organ weight persisted after cessation of dosing. Impaired female reproductive performance (decreased mating index, fertility index, and conception rate) was observed at the high dose. A no-effect dose for adverse developmental effects on preweaning rats was not identified. The lowest dose tested (0.75 mg/kg/day) was associated with plasma exposures (AUC) lower than that in humans at the maximum recommended human dose (MRHD) of 5 mg/day.

Oral administration of risdiplam (0, 1, 3, or 7.5 mg/kg/day) to young rats from PND 22 through PND 112 produced a marked increase in micronuclei in the bone marrow, male reproductive organ histopathology (degeneration/necrosis of the seminiferous tubule epithelium, oligo/aspermia in the epididymis, spermatocytic granulomas), and adverse effects on sperm parameters (decreased sperm concentration and motility, increased sperm morphology abnormalities) at the highest dose tested. Increases in T lymphocytes (total, helper, and cytotoxic) were observed at the mid and high doses. The reproductive and immune effects persisted after cessation of dosing. The no-effect dose (1 mg/kg/day) for adverse effects on postweaning juvenile rats was associated with plasma exposures (AUC) lower than that in humans at the MRHD.

## **9.5 GERIATRIC USE**

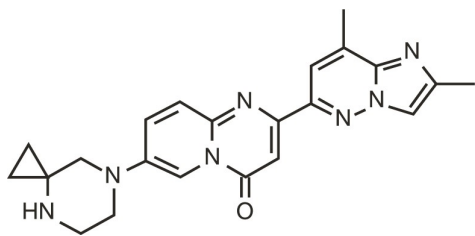
Clinical studies of EVRYSDI did not include patients aged 65 years and older to determine whether they respond differently from younger adult patients.

## **10. DESCRIPTION**

EVRYSDI for oral solution contains risdiplam, which is a survival of motor neuron 2 (SMN2)-directed RNA splicing modifier.

The chemical name of risdiplam is 7-(4,7-diazaspiro[2.5]octan-7-yl)-2-(2,8 dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido-4H-[1,2-a]pyrimidin-4-one. Risdiplam has a molecular weight of 401.46 g/mol.

The molecular formula of risdiplam is  $C_{22}H_{23}N_7O$  and the chemical structure is shown below.



EVRYSDI is supplied as a powder in an amber glass bottle. Each bottle contains 60 mg of risdiplam. The inactive ingredients of EVRYSDI are: Mannitol, Isomalt, Strawberry Flavor Tartaric Acid, Sodium Benzoate, Macrogol/Polyethylene Glycol 6000, Sucralose, Ascorbic Acid, Disodium Edetate Dihydrate

The powder is constituted with purified water to yield 60 mg/80 mL (0.75 mg/mL) of risdiplam after constitution [see *Dosage and Administration (2.4)*].

## **11. CLINICAL PHARMACOLOGY**

### **11.1 MECHANISM OF ACTION**

Risdiplam 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.

Using in vitro assays and studies in transgenic animal models of SMA, risdiplam was shown to increase exon 7 inclusion in SMN2 messenger ribonucleic acid (mRNA) transcripts and production of full-length SMN protein in the brain.

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.

## **11.2 PHARMACODYNAMICS**

In clinical trials for infantile-onset SMA and later-onset SMA patients, EVRYSDI led to an increase in SMN protein with a greater than 2-fold median change from baseline within 4 weeks of treatment initiation across all SMA types studied. The increase was sustained throughout the treatment period (of at least 24 months).

### Cardiac Electrophysiology

At the maximum recommended dose, clinically significant QTc interval prolongation was not observed.

## **11.3 PHARMACOKINETICS**

Pharmacokinetics of 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 once daily in a multiple-ascending-dose study in patients with SMA. Following once-daily oral administration of risdiplam 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.

### Absorption

Following oral administration of risdiplam in fasted state, the median time to reach maximum plasma concentration ( $T_{max}$ ) was 3.26 to 4 hours. The  $T_{max}$  was delayed by up to 1 hour in fed state compared to that under fasted state.

### *Effect of Food*

Food (high-fat, high calorie breakfast) had no relevant effect on the exposure of risdiplam. In the clinical efficacy studies (Study 1 and Study 2), risdiplam was administered with a morning meal or after breastfeeding.

### Distribution

The apparent volume of distribution at steady state is 190.4 L for a 31.3 kg patient.

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

### Elimination

The apparent clearance (CL/F) of risdiplam is 2.45 L/h for a 31.3 kg patient. The terminal elimination half-life of risdiplam was approximately 50 hours in healthy adults.

### *Metabolism*

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

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.

### *Excretion*

Following a dose of 18 mg, approximately 53% of the dose (14% unchanged risdiplam) was excreted in the feces and 28% in urine (8% unchanged risdiplam).

### Specific Populations

There were no clinically significant differences in the pharmacokinetics of EVRYSDI based on race or gender. Renal impairment is not expected to alter the exposures to risdiplam.

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

### *Hepatic Impairment*

The pharmacokinetics and safety of risdiplam have been studied in subjects with mild or moderate hepatic impairment (as defined by Child-Pugh class A and B, respectively,  $n = 8$  each) compared to subjects with normal hepatic function ( $n=10$ ). Following the administration of 5 mg EVRYSDI, the  $AUC_{inf}$  and  $C_{max}$  of risdiplam were approximately 20% and 5% lower, respectively, in subjects with mild hepatic impairment and were approximately 8% and 20% higher, respectively, in subjects with moderate hepatic impairment, versus matched healthy control subjects. The magnitude of these changes is not considered to be clinically meaningful. The pharmacokinetics and safety in patients with severe hepatic impairment (Child-Pugh class C) have not been studied.

### *Pediatric Patients*

Body weight and age were found to have significant effect on the pharmacokinetics of risdiplam. The estimated exposure (mean  $AUC_{0-24h}$ ) in pre-symptomatic infants at the age of 1 to 2 months was 2090 ng.h/mL at the recommended dose of 0.15 mg/kg once daily. The estimated exposure for infantile-onset SMA patients (age 2 to 7 months at enrollment) at the recommended dose of 0.2 mg/kg once daily was 1930 ng.h/mL. The estimated exposure for later-onset SMA patients (2 to 25 years old at enrollment) at the recommended dose was 2070 ng.h/mL (0.25 mg/kg once daily for patients with a body weight < 20 kg and 5 mg once daily for patients with a body weight  $\geq 20$  kg).

No data on risdiplam pharmacokinetics are available in patients less than 16 days of age [see *Use in Specific Populations* (9.4)].

### Drug Interaction Studies

#### *Effect of Other Drugs on EVRYSDI*

Coadministration of 200 mg itraconazole (a strong CYP3A inhibitor) twice daily with a single 6 mg oral dose of risdiplam did not have a clinically relevant effect on the pharmacokinetics of risdiplam (11% increase in AUC and 9% decrease in  $C_{max}$ ).

Risdiplam is a weak substrate of human MDR-1 and breast cancer resistant protein (BCRP) transporters in vitro. Human MDR-1 or BCRP inhibitors are not expected to result in a clinically significant increase of risdiplam concentrations.

#### *Effect of EVRYSDI on Other Drugs*

Risdiplam and its major circulating metabolite M1 did not induce CYP1A2, 2B6, 2C8, 2C9, 2C19, or 3A4 in vitro. Risdiplam and M1 did not inhibit (reversible or time-dependent inhibition) any of the CYP enzymes tested (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6), with the exception of CYP3A in vitro.

EVRYSDI is a weak inhibitor of CYP3A. 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%); this increase is not considered clinically relevant. Based on physiologically-based pharmacokinetic (PBPK) modeling, a similar increase is expected in children and infants as young as 2 months of age.

In vitro studies have shown that risdiplam and its major metabolite are not significant inhibitors of human MDR1, organic anion-transporting polypeptide (OATP) 1B1, OATP1B3, organic anion transporter 1 and 3 (OAT 1 and 3) transporters, and human organic cation transporter 2 (OCT2), at clinically relevant

concentrations. Risdiplam and its metabolite are, however, in vitro inhibitors of the multidrug and toxin extrusion (MATE) 1 and MATE2-K transporters [see *Drug Interactions* (8.1)].

## **12. NONCLINICAL TOXICOLOGY**

### **12.1 CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY**

#### Carcinogenesis

Risdiplam was not carcinogenic in Tg.rasH2 mice when administered at oral doses of up to 9 mg/kg/day for 26 weeks.

In a 2-year carcinogenicity study in rats, oral administration of risdiplam (0, 0.3, 1, or 3 mg/kg/day) resulted in increased incidences of preputial gland squamous cell carcinomas in males and combined thyroid follicular cell adenomas and carcinomas in females at the highest dose tested. The higher dose not associated with an increase in tumors (1 mg/kg/day) was associated with plasma drug exposures (AUC) similar to that in humans at the maximum recommended human dose (MRHD) of 5 mg/day.

#### Mutagenesis

Risdiplam was negative in an in vitro Ames assay. In an in vivo combined bone marrow micronucleus and comet assay in rat, risdiplam was clastogenic, as evidenced by an increase in micronuclei in bone marrow, but was negative in the comet assay. A pronounced increase in bone marrow micronuclei was also observed in toxicity studies in adult and juvenile rats [see *Use in Specific Populations* (9.4)].

#### Impairment of Fertility

Oral administration of risdiplam to rats for 4 (0, 1, 3, or 9 mg/kg/day) or 26 (0, 1, 3, or 7.5 mg/kg/day) weeks resulted in histopathological effects in the testis (degenerated spermatocytes, degeneration/atrophy of the seminiferous tubules) and epididymis (degeneration/necrosis of ductular epithelium) at the mid and/or high doses. At the high dose in the 26-week study, the testicular lesions persisted to the end of the recovery period, which corresponds, in rat, to approximately one spermatogenic cycle. The no-effect dose for adverse reproductive system effects in adult male rats (1 mg/kg/day) was associated with plasma drug exposures (AUC) similar to that in humans at the maximum recommended human dose (MRHD) of 5 mg/day.

Adverse effects of risdiplam on the testis could not be fully evaluated in the monkey because the majority of monkeys tested were sexually immature. However, oral administration of risdiplam (0, 2, 4, or 6 mg/kg/day) for 2 weeks resulted in histopathological changes in the testis (increases in multinucleate cells, germ cell degeneration) at the highest dose. At the no-effect dose for testicular toxicity in monkeys, plasma exposures were approximately 3 times that in humans at the MRHD.

Oral administration of risdiplam to postweaning juvenile rats resulted in male reproductive toxicity (degeneration/necrosis of the testis seminiferous epithelium with associated oligo/aspermia in the epididymis and abnormal sperm parameters). The no-effect dose for adverse reproductive effects in postweaning male juvenile rats was associated with plasma exposures approximately 4 times that in humans at the MRHD [see *Use in Specific Populations* (9.4)].

### **12.2 ANIMAL TOXICOLOGY AND/OR PHARMACOLOGY**

#### Retinal toxicity

Risdiplam-induced functional and structural retinal abnormalities were seen in animal studies. In a 39-week toxicity study in monkeys, oral administration of risdiplam (0, 1.5, 3, or 7.5/5 mg/kg/day; high dose lowered after 4 weeks) produced functional abnormalities on the electroretinogram (ERG) in all mid- and high-dose animals at the earliest examination time (Week 20). These findings were associated with retinal degeneration, detected by optical coherence tomography (OCT), on Week 22, the first examination time. The retinal degeneration, with peripheral photoreceptor loss, was irreversible. A no-effect dose for the retinal findings (1.5 mg/kg/day) was associated with plasma exposures (AUC) similar to that in humans at the maximum recommended human dose (MRHD) of 5 mg.

## Effect on Epithelial Tissues

Oral administration of risdiplam to rats and monkeys resulted in histopathological changes in epithelium of the gastrointestinal (GI) tract (apoptosis/single cell necrosis), lamina propria (vacuolation), the exocrine pancreas (single cell necrosis), the skin, tongue, and larynx (parakeratosis/hyperplasia/degeneration) with associated inflammation. The skin and GI epithelial effects were reversible. The no-effect doses for effects on epithelial tissues in rats and monkeys were associated with plasma exposures (AUC) similar to that in humans at the MRHD.

### **13. CLINICAL STUDIES**

The efficacy of EVRYSDI for the treatment of patients with infantile-onset, later-onset, and pre-symptomatic SMA was evaluated in three clinical studies, Study 1 (NCT02913482) and Study 2 (NCT02908685), and Study 3 (NCT03779334), respectively.

The overall findings of these studies support the effectiveness of EVRYSDI in SMA pediatric and adult patients and appear to support the early initiation of treatment with EVRYSDI.

#### **13.1 INFANTILE-ONSET SMA**

Study 1 was an open-label, 2-part study to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of EVRYSDI in patients with Type 1 SMA (symptom onset between 28 days and 3 months of age). 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.

Part 1 of Study 1 was designed as a dose-finding study. Part 2 of Study 1 assessed the safety and efficacy of EVRYSDI at 0.20 mg/kg, the recommended dose determined in Part 1 [see *Dosage and Administration* (2.4)]. Patients from Part 1 did not take part in Part 2.

A total of 62 patients with symptomatic Type 1 SMA were enrolled in FIREFISH Part 1 (n=21) and Part 2 (n=41), of which 58 patients received the recommended dosage [see *Dosage and Administration* (2.1)]. The median age of onset of clinical signs and symptoms was 1.5 months (range: 0.9 to 3.0 months). The median age at enrollment was 5.6 months (range: 2.2 to 6.9 months), and the median time between onset of symptoms and the first dose was 3.7 months (range 1.0 to 6.0 months). Of these patients, 60% were female, 57% were Caucasian, and 29% were Asian. The demographics and baseline disease characteristics were comparable between Part 1 and Part 2 of the study.

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 – Third 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 ( $\geq$  16 hours per day) or intubation, in the absence of an acute reversible event.

The primary endpoint was the proportion of patients with the ability to sit without support for at least 5 seconds (BSID-III gross motor scale, Item 22) after 12 months of treatment in Part 2; 29% of patients (n=12/41) achieved this milestone.

Other efficacy endpoints of EVRYSDI-treated patients in Study 1 (pooled Part 1 and Part 2) are shown in Table 3.

#### **Table 3 Key Efficacy Results at Month 12 and Month 24 (Study 1, Parts 1 and Part 2)**

| <b>Efficacy Endpoints</b>                                         | <b>Proportion of Patients<br/>Parts 1 &amp; 2 at Month 12</b> | <b>Proportion of Patients<br/>Parts 1 &amp; 2 at Month 24</b> |
|-------------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| Motor Function and Development Milestones                         | N = 58 <sup>a</sup>                                           |                                                               |
| BSID-III, Item 22: sitting without support for at least 5 seconds | 32.8%                                                         | 60.3%                                                         |
| Survival and Event-Free Survival                                  | N= 62 <sup>b</sup>                                            |                                                               |
| Alive without Permanent Ventilation                               | 87.1%                                                         | 83.8%                                                         |

<sup>a</sup> Results were pooled from all patients who received the recommended dose of risdiplam (all patients in Part 2 and those in the high-dose cohort of Part 1; n=58).

<sup>b</sup> Results were pooled from all patients who received any dose of risdiplam in Part 1 and Part 2 (n=62).

At Month 24, 40% (23/58) of patients who received the recommended dose achieved sitting without support for 30 seconds (BSID-III, Item 26). In addition at Month 24, patients continued to achieve additional motor milestones; 28% (16/58) of patients achieved a standing measure (16% [9/58] supporting weight and 12% [7/58] standing with support), as measured by Section 2 of the Hammersmith Infant Neurological Examination (HINE-2) which assesses motor milestones.

The proportion of patients alive without permanent ventilation (event-free survival) was 84% for all patients at Month 24 (Table 3). Out of 62 patients, 6 infants died (4 within the first 3 months following study enrollment) and one additional patient withdrew from treatment and died 3.5 months later. Four patients required permanent ventilation by Month 24. 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.

### **13.2 LATER-ONSET SMA**

Study 2 was a 2-part, multicenter trial to investigate the efficacy, safety, 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-blind, placebo-controlled, and is described below.

The primary endpoint in Study 2 Part 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).

Study 2 Part 2 enrolled 180 non-ambulatory patients with Type 2 (71%) or Type 3 (29%) SMA. Patients were randomized 2:1 to receive EVRYSDI at the recommended dosage [see *Dosage and Administration* (2.1)] or placebo. 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, 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 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 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 4 and Figure 1.

**Table 4 Summary of Efficacy in Patients with Later-Onset SMA at Month 12 of Treatment (Study 2 Part 2)**

| Endpoint                                                                                                              | EVRYSDI<br>(N = 120)                 | Placebo<br>(N = 60) |
|-----------------------------------------------------------------------------------------------------------------------|--------------------------------------|---------------------|
| Primary Endpoint:                                                                                                     |                                      |                     |
| Change from baseline in total MFM32 score at Month 12, LS means (95% CI) <sup>1,2,3</sup>                             | 1.36 (0.61, 2.11)                    | -0.19 (-1.22, 0.84) |
| Difference from Placebo, Estimate (95% CI) <sup>1</sup><br>p-value                                                    | 1.55 (0.30, 2.81)<br>0.0156          |                     |
| Secondary Endpoints:                                                                                                  |                                      |                     |
| Proportion of patients with a change from baseline MFM32 total score of 3 or more at Month 12 (95% CI) <sup>2,3</sup> | 38.3% (28.9, 47.6)                   | 23.7% (12.0, 35.4)  |
| Odds ratio for overall response (95% CI) adjusted <sup>4</sup> (unadjusted) p-value <sup>5</sup>                      | 2.35 (1.01, 5.44)<br>0.0469 (0.0469) |                     |
| Change from baseline in total score of RULM at Month 12, LS means (95% CI) <sup>1, 6</sup>                            | 1.61 (1.00, 2.22)                    | 0.02 (-0.83, 0.87)  |
| Difference from Placebo, Estimate (95% CI) adjusted <sup>4</sup> (unadjusted) p-value <sup>1</sup>                    | 1.59 (0.55, 2.62)<br>0.0469 (0.0028) |                     |

1. The Mixed Model Repeated Measure (MMRM) analysis included the change from baseline total score as the dependent variable and as independent variables the baseline total score, treatment group, time, treatment-by-time interaction, and the randomization stratification variable of age group (2 to 5, 6 to 11, 12 to 17, 18 to 25).

2. The MFM total score was calculated according to the user manual, expressed as a percentage of the maximum score possible for the scale (i.e., sum of the 32 item scores divided by 96 and multiplied by 100).

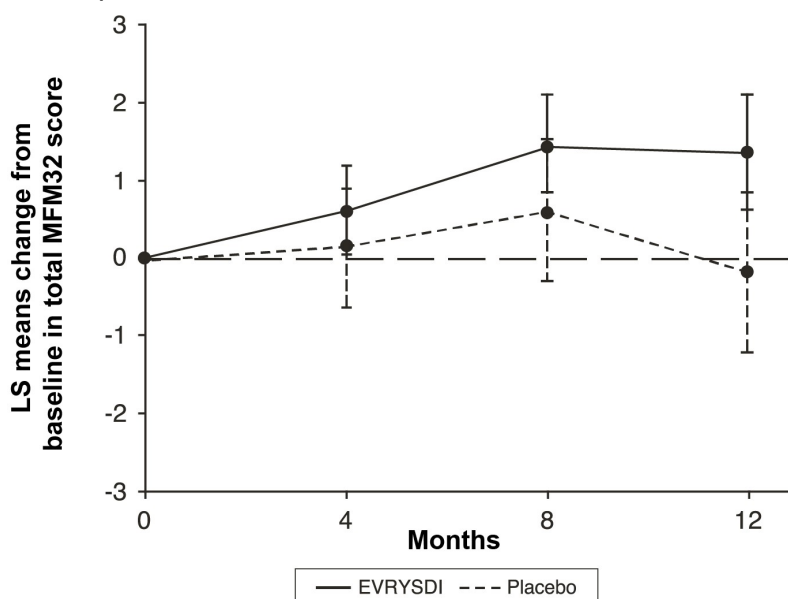
3. Based on the missing data rule for MFM32, 6 patients were excluded from the analysis (EVRYSDI n = 115; placebo control n = 59).

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.

5. The logistic regression analysis included the baseline total score, treatment and age group as independent variables.

6. Based on the missing data rule for RULM, 3 patients were excluded from the analysis (EVRYSDI n = 119; placebo control n = 58).

**Figure 1 Mean Change from Baseline in Total MFM32 Score Over 12 Months (Study 2 Part 2)<sup>1,2</sup>**



<sup>1</sup> Error bars denote the 95% confidence interval.

<sup>2</sup> The MFM total score was calculated according to the user manual, expressed as a percentage of the maximum score possible for the scale (i.e., sum of the 32 item scores divided by 96 and multiplied by 100).

### 13.3 PRE-SYMPTOMATIC SMA

Study 3 was an open-label, single-arm, multicenter clinical study to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of EVRYSDI in infants up to 6 weeks of age (at first dose) who have been genetically diagnosed with SMA but do not yet present with symptoms.

The efficacy in pre-symptomatic SMA patients was evaluated at Month 12 in 26 patients treated with EVRYSDI in Study 3: 8 patients had 2 copies of the *SMN2* gene, 13 patients had 3 copies, and 5 patients had 4 or more copies. The median age of these patients at first dose was 25 days (range: 16 to 41), 62% were female, and 85% were Caucasian. The primary efficacy population (N = 5) included patients with 2 *SMN2* copies and a baseline CMAP amplitude  $\geq 1.5$  mV.

The primary efficacy endpoint was the proportion of patients with the ability to sit without support for at least 5 seconds (BSID-III gross motor scale, Item 22) at Month 12. This milestone was achieved by 80% (4/5) of patients in the primary efficacy population. This milestone was also achieved by 87.5% (7/8) of all patients with 2 copies of *SMN2* and 96.2% (25/26) of patients in the full treated population.

At Month 12, 80.8% (21/26) of patients in the full treated population achieved sitting without support for 30 seconds (BSID-III, Item 26). Of the 26 patients treated with EVRYSDI, 25 patients had motor milestones measured by the HINE-2 at Month 12. Of these, 24 (96%) achieved sitting (23 patients could pivot/rotate and 1 achieved stable sit); 21 (84%) could stand (13 patients could stand unaided and 8 could stand with support); and 12 (48%) could walk independently. Seven patients were not tested for walking at Month 12. All 26 patients were alive at 12 months without permanent ventilation.

## 14. PHARMACEUTICAL PARTICULARS

### 14.1 STORAGE

#### Storage

Powder for Oral Solution: Do not store above 25°C.

Keep in the original amber bottle.

After constitution, the oral solution should be stored in the refrigerator (2°C to 8°C) for up to 64 days. If necessary, the patient or their caregiver may store the oral solution at room temperature (below 40°C) for no more than a total combined time of 5 days. Do not freeze. Do not store the oral solution above 40°C. Keep the oral solution in the original bottle and keep the bottle always in an upright position with the cap tightly closed.

### Shelf life

This medicine should not be used and should be discarded:

- after the expiry date (“EXP” for the powder, and “Discard After” for the constituted oral solution) on the pack and on the bottle.
- if the oral solution is kept outside of the refrigerator for more than a total combined time of 5 days at room temperature (below 40°C),
- or if the oral solution is kept above 40°C.

## 14.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

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

EVERYSDI powder must be constituted to the oral solution by a healthcare professional prior to being dispensed.

Caution should be exercised in the handling of EVERYSDI powder for oral solution (see *Section 5 Warnings and Precautions*). Avoid inhalation and avoid direct contact with skin or mucous membranes with the dry powder and the constituted solution.

Wear disposable gloves during constitution and while wiping the outer surface of the bottle/cap and cleaning the working surface after constitution. If contact occurs, wash thoroughly with soap and water; rinse eyes with water.

### Selecting the Oral Syringe for the Prescribed Daily Dose

**Table 5** Selecting the Oral Syringe for the Prescribed Daily Dose of EVERYSDI

| Syringe Size | Dosing Volume  | Syringe Markings |
|--------------|----------------|------------------|
| 1mL          | 0.3mL to 1.0mL | 0.01mL           |
| 6mL          | 1.0mL to 6.0mL | 0.1mL            |
| 12mL         | 6.2mL to 6.6mL | 0.2mL            |

For the calculation of dosing volume, the syringe markings need to be considered. Round the dose volume to the nearest graduation mark on the selected oral syringe.

### Instructions for administration

#### *Dosing of EVERYSDI oral solution (0.75 mg/mL)*

Refer to *Section 2.1 Dosage and Administration* for the proper dosing regimen instructions.

*For detailed instructions on constitution and administration please refer to the Instructions for Use and Instructions for Constitution (TEC-0155570, Version 10.0).* If it is not taken within 5 minutes, the dose should be discarded and a new dose should be prepared.

### Incompatibilities

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

### **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.

## **15. PATIENT COUNSELING INFORMATION**

Advise the patient to read the Instructions for Use.

### Pregnancy and Fetal Risk

Inform pregnant women and women of reproductive potential that, based on animal studies, EVRYSDI may cause fetal harm [see *Use in Specific Populations* (9.1)].

Discuss with women of childbearing age whether they are pregnant, might be pregnant, or are trying to become pregnant.

Advise women of childbearing potential to use effective contraception during treatment with EVRYSDI and for at least 1 month after stopping EVRYSDI.

Advise a female patient to immediately inform the prescriber if she is pregnant or planning to become pregnant [see *Use in Specific Populations* (9.3)].

### Potential Effects on Male Fertility

Advise male patients that their fertility may be compromised while on treatment with EVRYSDI [see *Use in Specific Populations* (9.3)].

### Instructions for Preparation of Oral Solution

Advise patients/caregivers to ensure that EVRYSDI is in liquid form when received from the pharmacy.

Instruct patients/caregivers to take EVRYSDI with or without food or before or after breastfeeding at approximately the same time each day. However, instruct caregivers not to mix EVRYSDI with formula or milk.

Instruct patients/caregivers to take EVRYSDI immediately after it is drawn up into the reusable oral syringe [see *Dosage and Administration* (2.1)].

|                                                |
|------------------------------------------------|
| <b>Medicine: keep out of reach of children</b> |
|------------------------------------------------|

**Version: MYEvrySDI20260413CDS13.0**

Revision date: April 2026

Made in Switzerland by  
F. Hoffmann-La Roche Ltd, Basel  
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**INSTRUCTION FOR CONSTITUTION (0.75 mg/mL)**  
**EVERYSOI (risdiplam) for oral solution**

Instructions for Constitution

**(FOR HEALTHCARE PROFESSIONALS ONLY)**

**Each EVRYSOI carton contains (See figure A):**

- 1.** 1 Cap
- 2.** 1 EVRYSOI bottle
- 3.** 1 Oral syringe 12 mL (in a pouch)
- 4.** 2 Oral syringes 6 mL (in pouches)
- 5.** 2 Oral syringes 1 mL (in pouches)
- 6.** 1 Press-in bottle adapter
- 7.** 1 Package Leaflet (not shown)
- 8.** 1 Instructions for Constitution (not shown)
- 9.** 1 Instructions for Use (not shown)

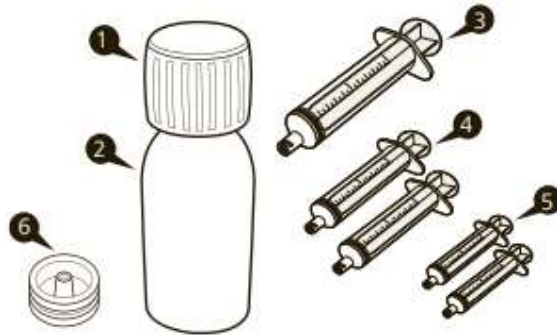


Figure A

**Important information about EVRYSOI**

- **Avoid inhaling** EVRYSOI 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 constituted 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 constitute the medicine.
- Do not add oral syringes other than the ones provided in the carton.

**How to store EVRYSOI**

- Store the powder (unconstituted medicine) at room temperature, below 25°C (77°F) and keep it in the carton.
- Store the solution (constituted medicine) in a refrigerator between 2°C to 8°C (35°F to 46°F).
- Keep the oral solution in the original bottle and always keep the bottle in an upright position with the cap tightly closed.

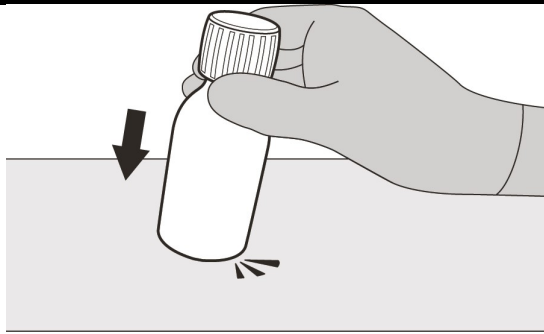


Figure B

**Step 1**

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

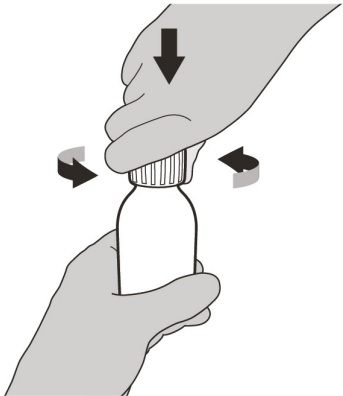


Figure C

**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).

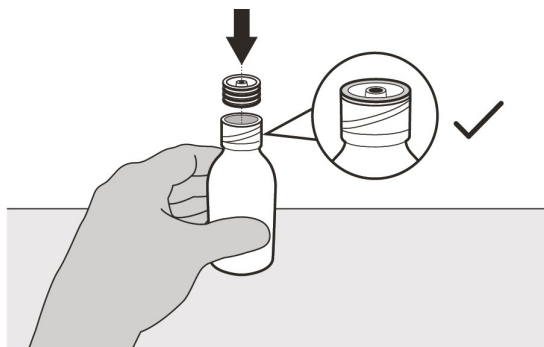


Figure E

**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).

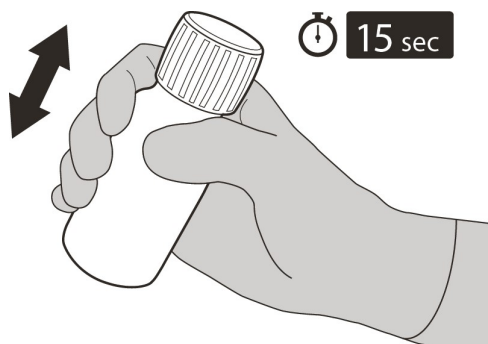


Figure F

#### 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**.

Afterwards, shake well again for another 15 seconds.



Figure G

#### Step 6

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

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

Put the bottle **back in its original carton**, with syringes (in pouches), Package Leaflet and Instructions For Use booklet. Store the carton into the refrigerator.

### EVRYSDI (risdiplam)

EVRYSDI is a trademark of Hoffmann-La-Roche AG.

TEC-0155570, Version 10.0

## **INSTRUCTION FOR USE – ADMINISTRATION (0.75 mg/mL)**

### **EVERYSDI (risdiplam) for oral solution**

#### **Instructions for Use**

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

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

EVERYSDI 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.

#### **Important information about EVERYSDI**

- 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 pack to measure your prescribed daily dose. The oral syringe protects the medicine from light.
- Contact your healthcare provider if your oral syringe(s) 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 daily dose of EVERYSDI”** for the correct oral syringe you should use. Ask your healthcare professional if you have questions on how to select the right oral syringe.
- If the bottle adapter is not in the bottle, **do not** use EVERYSDI and then contact your healthcare professional.
- **Do not** use EVERYSDI after the **Discard after** date written on the bottle label. Ask your healthcare professional for the **Discard after** date if it is not written on the bottle label.
- **Do not** mix EVERYSDI into food or liquids (eg. milk or formula milk).
- **Do not** use EVERYSDI if the bottle or oral syringes are damaged.
- **Avoid** getting EVERYSDI on your skin. If EVERYSDI gets on your skin, wash the area with soap and water.
- If you spill EVERYSDI, 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 EVERYSDI left in the bottle for your prescribed dose, discard the bottle with remaining EVERYSDI and used oral syringes according to your local requirements; use a new bottle of EVERYSDI to obtain your prescribed daily dose. **Do not mix** EVERYSDI from the new bottle with the bottle you are currently using.

**Each EVRYSDI carton contains (See figure A):**

- 1.** 1 EVRYSDI bottle with bottle adapter and cap
- 2.** 1 Oral syringe 12 mL (in a pouch)
- 3.** 2 Oral syringes 6 mL (in pouches)
- 4.** 2 Oral syringes 1mL (in pouches)
- 5.** 1 Instructions for Use booklet (not shown)
- 6.** 1 Package Leaflet (not shown)

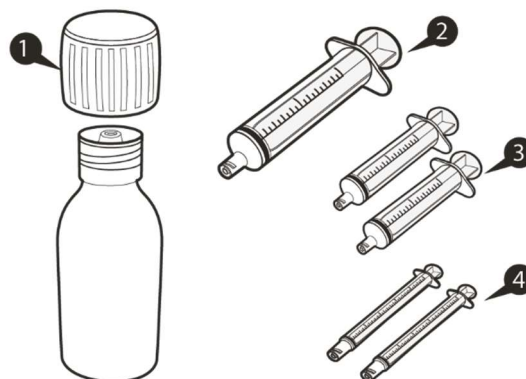


Figure A

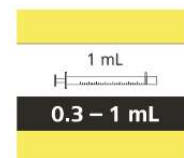
**How to store EVRYSDI**

Please see section 14.1 Storage of the Pack Insert for full information.

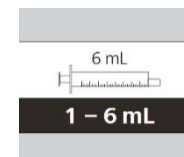
**A) Preparing and withdrawing your daily dose**

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

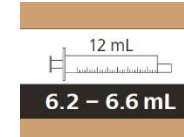
- If your prescribed daily dose of EVRYSDI is between 0.3 mL and 1 mL, use a 1 mL oral syringe (yellow label).



- If your prescribed daily dose of EVRYSDI is between 1 mL and 6 mL, use a 6 mL oral syringe (grey label).



- If your prescribed daily dose of EVRYSDI is 6.2 mL or higher, use a 12 mL oral syringe (brown label).



Ask your HCP about rounding you or your child's daily dose to the nearest syringe marking.

**How to prepare your daily dose of EVRYSDI**

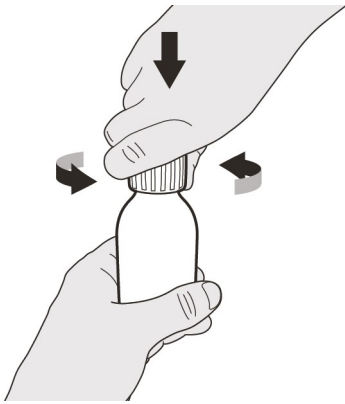


Figure B

#### 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.

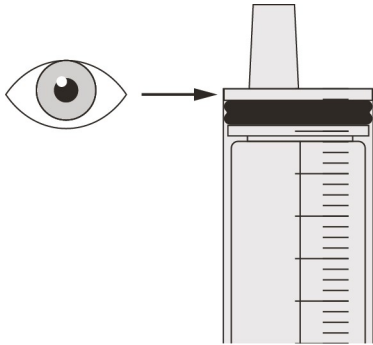


Figure C

#### Step A2

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

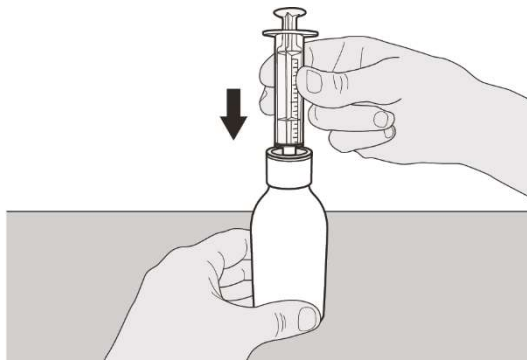


Figure D

#### Step A3

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

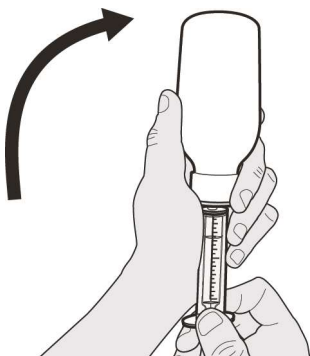


Figure E

#### Step A4

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

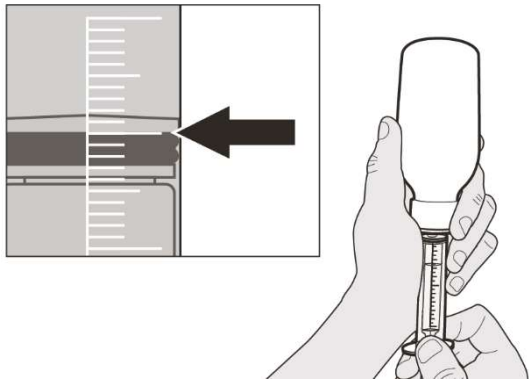


Figure F

#### Step A5

Slowly pull back on the plunger to withdraw your prescribed daily 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.**

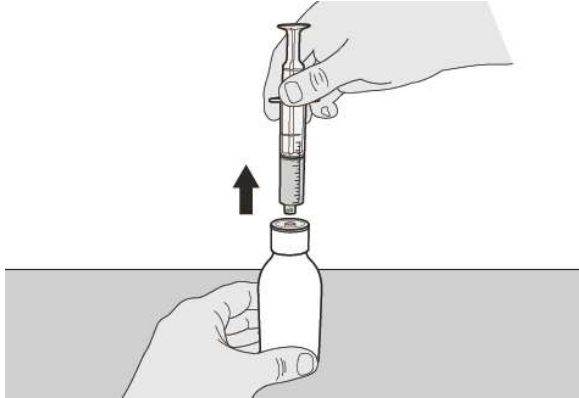


Figure G

#### 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).

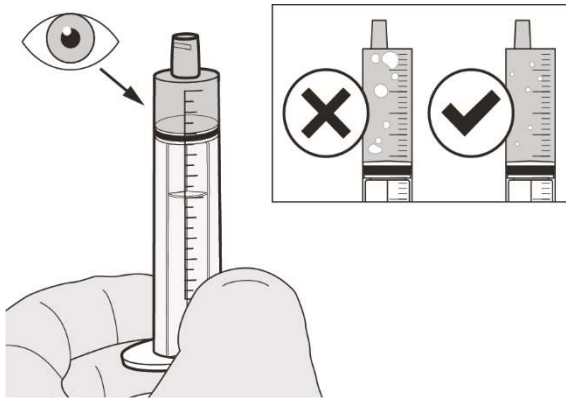


Figure H

#### 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 daily 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.

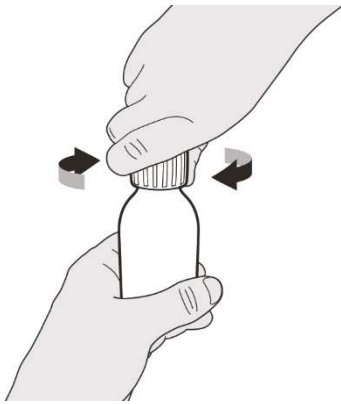


Figure I

#### 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 your daily dose of EVRYSDI by mouth, follow the instructions in **“B) How to take a daily dose of EVRYSDI by mouth”**.

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

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

EVRYSDI’s oral syringes are specifically designed to be compatible with the ENFit® system. If your feeding tube is not ENFit® compatible, you may need an ENFit® transition connector to connect the EVRYSDI syringe to your G-tube or NG-tube.

### B) How to take a daily dose of EVRYSDI by mouth

Sit upright when taking a daily 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.**

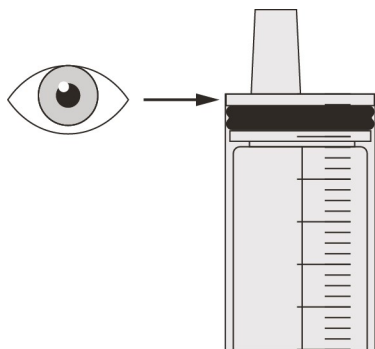


Figure K

### Step B2

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



Figure L

### Step B3

**Drink** some water right after taking the prescribed dose of EVRYSDI (See Figure L).

**Go to Step E for cleaning of the syringe.**

## C) How to give a daily 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.

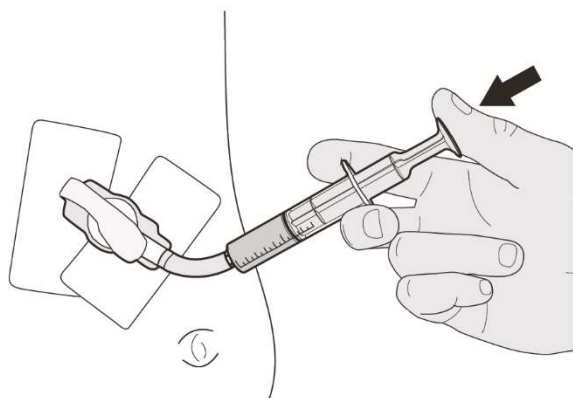


Figure M

### 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).

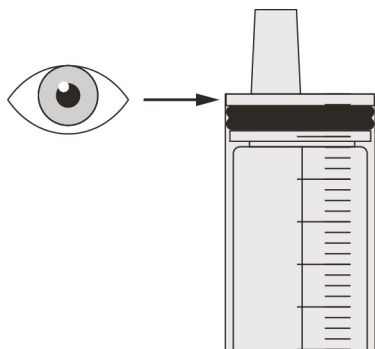


Figure N

### Step C2

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

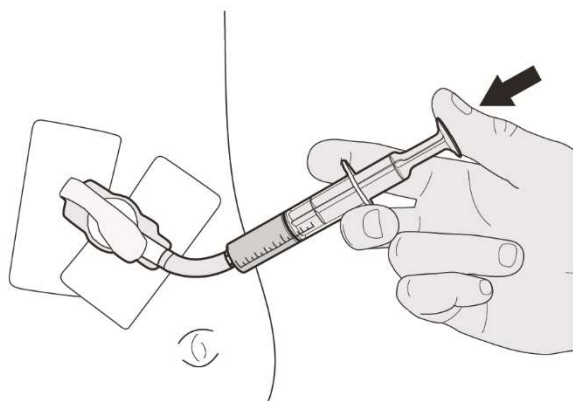


Figure O

### 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 daily 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.

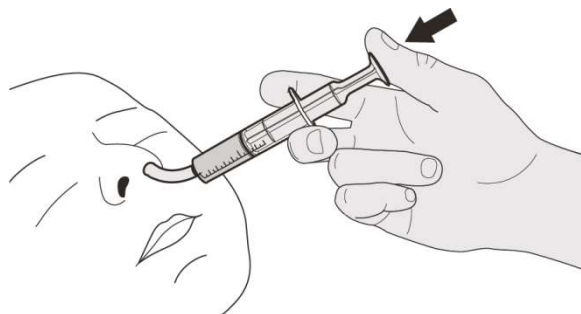


Figure P

### 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).

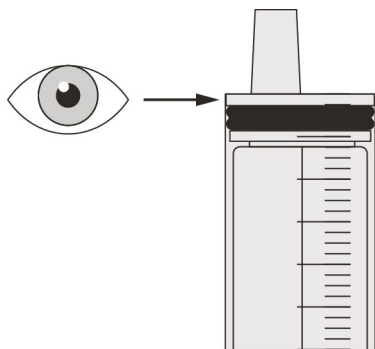


Figure Q

### Step D2

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

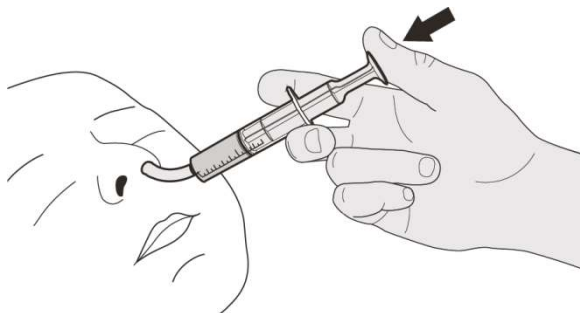


Figure R

### 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

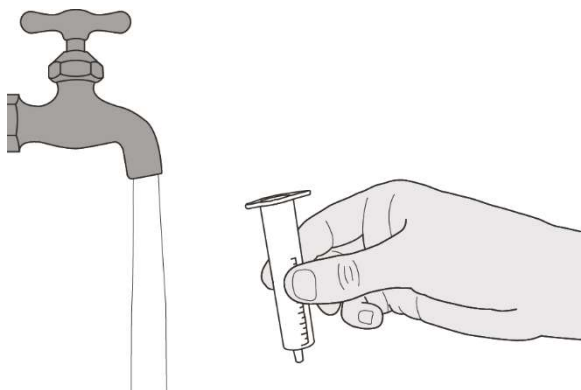


Figure S

### Step E1

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

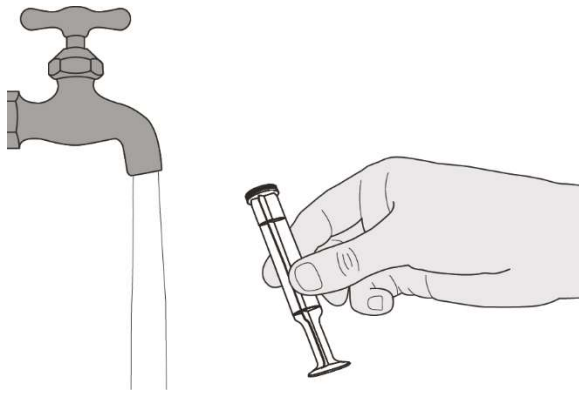


Figure T

**Step E2**

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

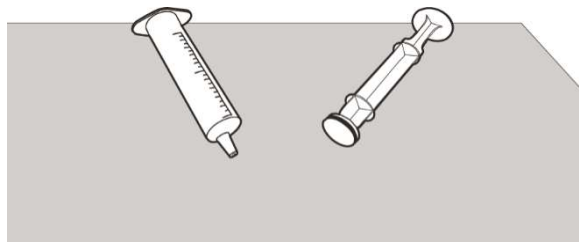


Figure U

**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.

**EVERYSDI (risdiplam)**

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