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**POWSOL/TAB-EVR-2026 02**

# EVRYSDI®

Risdiplam

## 1. DESCRIPTION

### 1.1 THERAPEUTIC / PHARMACOLOGIC CLASS OF DRUG

Pharmacotherapeutic group: Other drugs for disorders of the musculo-skeletal system
ATC code: M09AX10

### 1.2 TYPE OF DOSAGE FORM

Powder for oral solution: Oral or enteral

Film-coated tablet: Oral

### 1.3 ROUTE OF ADMINISTRATION

Oral or enteral

### 1.4 STERILE / RADIOACTIVE STATEMENT

Not applicable

### 1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: risdiplam

***Evrysdi Powder for oral solution:***
Evrysdi powder for oral solution is supplied as a powder in a 100 mL, Type III amber glass bottle. Each bottle is filled with 2.0 g of powder containing 60 mg of risdiplam.

The powder is constituted with purified water or water for injection to yield an oral solution containing 0.75 mg/mL of risdiplam (see section *4.2 Special Instructions for Use, Handling and Disposal*).

Excipients: Ascorbic Acid, Disodium Edetate Dihydrate, Isomalt, Macrogol/Polyethylene Glycol 6000, Mannitol, Sodium Benzoate, Strawberry Flavor, Sucralose, Tartaric Acid

***Evrysdi Film-coated tablet:***
Each Evrysdi film-coated tablet contains 5 mg of risdiplam.

Evrysdi 5mg film-coated tablet is a round and curved, pale yellow tablet, with EVR debossed on one side.

Excipients:
*Tablet core:* Tartaric acid, Mannitol, Microcrystalline cellulose, Silica, colloidal anhydrous, Crospovidone, Sodium Stearyl Fumarate, Strawberry Flavor.
*Film coat:* Polyvinyl Alcohol, Titanium dioxide, Macrogol/Polyethlene Glycol 3350, Talc, Yellow Iron Oxide

## 2. CLINICAL PARTICULARS

### 2.1 THERAPEUTIC INDICATION(S)

Evrysdi is indicated for the treatment of spinal muscular atrophy (SMA).

### 2.2 DOSAGE AND ADMINISTRATION

**General**
SMA treatment should be initiated as early as possible after diagnosis.

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

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

***Evrysdi Powder for Oral Solution***
Evrysdi powder for oral solution must be constituted by a health care provide (HCP) prior to being dispensed.

Evrysdi powder for oral solution is available for all age groups.

***Evrysdi Film-coated Tablets***
The Evrysdi film-coated tablets are available for patients prescribed the 5 mg dose.

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

| *Age[a] and Body Weight* | *Recommended Daily Dose* | *Dosage Form* |
|---|---|---|
| < 2 months of age | 0.15 mg/kg | Powder for oral solution |
| 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 | Powder for oral solution or Film-coated tablet |

[a] based on corrected age for preterm infants

The physician should prescribe the appropriate pharmaceutical form according to the dose required, and the patient's needs. For patients with difficulty swallowing a whole tablet, the tablet can be dispersed or the powder for oral solution can be prescribed.

Dose changes must be made under the supervision of an HCP. Treatment with a daily dose above 5 mg has not been studied. Limited post marketing data are available in infants below 16 days of age (see section 3.2.5 *Pharmacokinetics in Special Populations*).

**Method of administration**
It is recommended a HCP discuss with the patient or caregiver how to prepare the prescribed daily dose prior to administration of the first dose (see section *4.2 Special Instruction for Use, Handling and Disposal*).

***Evrysdi Powder for oral solution:***
Use the re-usable oral syringe provided to deliver the daily dose of Evrysdi powder for oral solution.

The patient should drink water after taking the constituted Evrysdi powder for oral solution to ensure the drug has been completely swallowed. If the patient is unable to swallow and has a nasogastric or gastrostomy tube, administer Evrysdi powder for oral solution via the tube. The tube should be flushed with water after delivering Evrysdi powder for oral solution (see section *4.2 Special Instructions for Use, Handling and Disposal*).

***Evrysdi Film-coated tablet:***
The Evrysdi film-coated tablet should be swallowed whole with water or dispersed in a small amount of room temperature non-chlorinated drinking water (e.g. bottled water) (see section 4.2 Special Instruction for Use, Handling and Disposal). Do not chew, cut or crush the tablets.

If Evrysdi film-coated tablet is dispersed in non-chlorinated drinking water (e.g. bottled water), take it immediately. Evrysdi film-coated tablets must not be dispersed in any liquid other than non-chlorinated drinking water (e.g. bottled water). Discard the prepared dispersion if it is not used within 10 minutes of adding water. Do not expose the prepared dispersion to sunlight.

If the prepared dispersion spills or gets on the skin, the area should be washed with soap and water.

Evrysdi film-coated tablets should not be administered via nasogastric or gastrostomy tube. If administration through a nasogastric or gastrostomy tube is required, the Evrysdi powder for oral solution should be used.

**Delayed or Missed Doses**
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 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.

#### 2.2.1 Special Dosage Instructions

**Pediatric use**
The safety and efficacy of Evrysdi in pediatric patients < 16 days of age have not yet been established in clinical trials (see section *3.1.2 Clinical / Efficacy Studies*). Limited safety data are available from the post marketing setting from patients below 16 days of age treated with Evrysdi at the recommended dose. The safety and efficacy of Evrysdi in preterm infants before reaching the corrected age of 16 days have not been established.

**Geriatric use**
The pharmacokinetics (PK) and safety of Evrysdi have been assessed in subjects without SMA up to 69 years of age. Evrysdi has not been studied in patients with SMA above 60 years of age (see sections *3.2.5 Pharmacokinetics in Special Populations* and *2.5.5 Geriatric Use*).

**Renal Impairment**
The safety and efficacy of Evrysdi in patients with renal impairment have not been studied. No dose adjustment is expected to be required in patients with renal impairment (see sections *3.2.5 Pharmacokinetics in Special Populations* and *2.5.6 Renal Impairment*).

**Hepatic Impairment**
No dose adjustment is required in patients with mild or moderate hepatic impairment. Evrysdi has not been studied in patients with severe hepatic impairment (see sections *3.2.5 Pharmacokinetics in Special Populations* and *2.5.7 Hepatic Impairment*).

### 2.3 CONTRAINDICATIONS

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

### 2.4 WARNINGS AND PRECAUTIONS

#### 2.4.1 General

**Embryo-fetal Toxicity**
Embryo-fetal toxicity has been observed in animal studies (see section *3.3 Nonclinical Safety*). 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 *2.5 Use in Special 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 *2.5 Use in Special Populations* and *3.3.3 Impairment of Fertility*).

#### 2.4.2 Drug Abuse and Dependence

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

#### 2.4.3 Ability to Drive and Use Machines

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

### 2.5 USE IN SPECIAL POPULATIONS

**Use with SMA gene therapy**
Efficacy data of Evrysdi treatment when used in patients that previously received SMN1 gene therapy is not available.

#### 2.5.1 Females and Males of Reproductive Potential

**Fertility**
*Male patients*
Male fertility may be compromised while on treatment with Evrysdi based on nonclinical findings. In rat and monkey reproductive organs, sperm degeneration and reduced sperm numbers were observed (see *section 3.3.3 Impairment of Fertility*). The effects on sperm cells are reversible upon discontinuation of risdiplam.
Prior to initiating treatment with Evrysdi, fertility preservation strategies should be discussed with male patients receiving Evrysdi. 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 Evrysdi for a minimum of 4 months. Treatment may be re-started after conception.

*Female patients*
Based on nonclinical data, an impact of Evrysdi on female fertility is not expected (see section *3.3.3 Impairment of Fertility*).

**Pregnancy testing**
The pregnancy status of females of reproductive potential should be verified prior to initiating Evrysdi therapy. Pregnant women should be clearly advised of the potential risk to the fetus.

**Contraception**
Male and female patients of reproductive potential should adhere to the following contraception requirements:

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

#### 2.5.2 Pregnancy

There are no clinical data from the use of Evrysdi in pregnant women. Risdiplam has been shown to be embryo-fetotoxic and teratogenic in animals. Based on the findings from animal studies, risdiplam crosses the placental barrier and may cause fetal harm (see section *3.3.4 Reproductive toxicity*).

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 should be clearly advised on the potential risk to the fetus.

The safe use of Evrysdi during labor and delivery has not been established.

#### 2.5.3 Lactation

It is not known whether Evrysdi is excreted in human breast milk. Studies in rats show that risdiplam is excreted into milk (see section *3.3.4 Reproductive toxicity*). 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.

#### 2.5.4 Pediatric Use

(See sections *2.1 Therapeutic Indication(s), 2.2 Dosage and Administrations, 3.1.2 Clinical / Efficacy Studies, 3.2.5 Pharmacokinetics in Special Populations, 2.6 Undesirable Effects* and *3.3.5 Other, Juvenile animal studies.*)

#### 2.5.5 Geriatric Use

The PK and safety of Evrysdi have been studied in subjects without SMA up to 69 years of age. Evrysdi has not been studied in patients with SMA above 60 years of age (see sections *3.2.5 Pharmacokinetics in Special Populations* and *3.1.2 Clinical Studies*).

#### 2.5.6 Renal Impairment

The safety and efficacy of Evrysdi in patients with renal impairment have not been studied. A change in dose is not expected to be required for patients with renal impairment (see sections *2.2.1 Special Dosage Instructions, 3.2.3 Metabolism, 3.2.4 Elimination*, and *3.2.5 Pharmacokinetics in Special Populations*).

#### 2.5.7 Hepatic Impairment

The PK, safety and tolerability of a single dose of 5 mg risdiplam were evaluated in subjects with mild or moderate hepatic impairment in a dedicated clinical study. Mild or moderate hepatic impairment had no impact on the PK of risdiplam. No dose adjustment is therefore required in patients with mild or moderate hepatic impairment. Evrysdi has not been studied in patients with severe hepatic impairment (see sections *2.2.1 Special Dosage Instructions* and *3.2.5 Pharmacokinetics in Special Populations*).

### 2.6 UNDESIRABLE EFFECTS

#### 2.6.1 Clinical Trials

**Summary of the safety profile**
The safety profile of Evrysdi is based on four clinical trials FIREFISH, SUNFISH, RAINBOWFISH and JEWELFISH.

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. The median exposure duration was 27.8 months (range: 0.6 to 46.5 months) (see section *3.1.2 Clinical / Efficacy Studies*). The adverse drug reactions (ADRs) observed in clinical trials for infantile-onset SMA in Table 2 are based on the pooled analysis of patients from FIREFISH Part 1 and 2. ADRs are defined as adverse events occurring in ≥ 5% of patients and where a causal association with Evrysdi is possible.

The SUNFISH study is a two-part study with later-onset SMA between 2-25 years of age (see section *3.1.2 Clinical / Efficacy Studies*). The ADRs observed in clinical trials for later-onset SMA in Table 3 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. ADRs are defined as adverse events occurring in ≥ 5% of Evrysdi treated patients which occurred ≥ 5% more frequently or at least 2 times as frequently as in placebo control patients and where a causal association with Evrysdi is possible.

In infantile-onset SMA patients, the most common adverse reactions observed in Evrysdi clinical studies were pyrexia (48.4%), rash (27.4%) and diarrhoea (16.1%).

In later-onset SMA patients, the most common adverse reactions observed in Evrysdi clinical studies were pyrexia (21.7%), headache (20.0%), diarrhoea (16.7%), and rash (16.7%).

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

| System Organ Class | Adverse Reaction | Incidence N=62 n (%) | Number of events/ 100 patient years Total exposure in patient years = 142.4 | Frequency Category |
|---|---|---|---|---|
| Gastrointestinal Disorders | Diarrhea | 12 (19.4) | 9.8 | Very common |
| Skin and Subcutaneous Tissue Disorders | Rash* | 18 (29.0) | 16.2 | Very common |

* Includes dermatitis, dermatitis acneiform, dermatitis allergic, erythema, folliculitis, rash, rash erythematous, rash maculo-papular, rash papular

**Table 3 Summary of adverse drug reactions for later-onset SMA patients observed in SUNFISH Part 2 study**

| System Organ Class | Adverse Reaction | Evrysdi N=120 n (%) | Placebo N=60 n (%) | Frequency Category |
|---|---|---|---|---|
| Gastrointestinal Disorders | Diarrhea | 20 (16.7) | 5 (8.3) | Very common |
| Skin and Subcutaneous Tissue Disorders | Rash* | 20 (16.7) | 1 (1.7) | Very common |

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

The adverse reactions diarrhea and rash occurred without an identifiable time or clinical pattern and resolved despite ongoing treatment with Evrysdi in infantile-onset and later-onset SMA patients. These events are not suggestive of the effect on epithelial tissues observed in animal studies (see section *3.3.5 Nonclincal Safety*).

The RAINBOWFISH study is an open-label, single-arm study that enrolled 26 patients with pre-symptomatic SMA between 16 and 41 days of age at first dose. At the time of primary analysis, the median exposure duration was 20.4 months (range: 10.6 to 41.9 months) (see section *3.1.2 Clinical / Efficacy Studies*). The safety profile of Evrysdi in pre-symptomatic patients in the RAINBOWFISH study is consistent with the safety profile for symptomatic SMA patients treated with Evrysdi in clinical trials.

*Safety Profile in Patients Previously Treated with Other SMA Modifying Therapies*
Based on the primary analysis of the JEWELFISH study, the safety profile of Evrysdi in treatment non-naive patients who received Evrysdi for up to 59 months (including those previously on treatment with nusinersen (n=76) or with onasemnogene abeparvovec (n=14)) is consistent with the safety profile for treatment naive SMA patients treated with Evrysdi in the FIREFISH (Part 1 and Part 2), SUNFISH (Part 1 and Part 2), and RAINBOWFISH studies. (see section *3.1.2 Clinical / Efficacy Studies*).

#### 2.6.2 Postmarketing Experience

The following adverse drug reactions have been identified from postmarketing experience with Evrysdi (Table 4). Adverse drug reactions are listed according to system organ classes in MedDRA and the corresponding frequency category estimation for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

**Table 4 Adverse drug reactions from postmarketing experience**

| System Organ Class | Adverse Reaction | Frequency Category |
|---|---|---|
| Skin and subcutaneous disorders | Cutaneous vasculitis[1] | Unknown |
| Cardiac disorders | Tachycardia[2] | Uncommon |

[1] Incidence rate and frequency category cannot be estimated based on available data
[2] The frequency category for ADRs observed only in the postmarketing setting is defined as the upper limit of the 95% confidence interval calculated on the basis of the total number of patients exposed to Evrysdi in pivotal trials.

***Description of selected adverse drug reactions from postmarketing experience***
Cutaneous vasculitis - Symptoms recovered after permanent discontinuation of Evrysdi.

Tachycardia – Symptoms resolved after interruption of Evrysdi and restarted following retreatment with Evrysdi.

### 2.7 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.

### 2.8 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Risdiplam is primarily metabolized by flavin monooxygenase 1 and 3 (FMO1 and 3), and also by CYPs 1A1, 2J2, 3A4 and 3A7. Risdiplam is not a substrate of human multidrug resistance protein 1 (MDR1).

**Effects of other medicinal products on Evrysdi**
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 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.

No drug-drug interactions are expected via the FMO1 and FMO3 pathway.

Omeprazole had no impact on the pharmacokinetics of risdiplam administered as a tablet. The risdiplam tablet may therefore be administered concomitantly with medication that increases the gastric pH (proton pump inhibitors, H2 antagonists, and antacids).

**Effects of Evrysdi on other medicinal products**
*In vitro* 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.

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 (11% increase in AUC; 16% increase in $C_{max}$). The extent of the interaction is not considered clinically relevant, and therefore no dose adjustment is required for CYP3A substrates. Based on physiologically based pharmacokinetic

(PBPK) modelling a similar magnitude of the effect is expected in children and infants as young as 2 months old.

*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). Risdiplam and its metabolite are, however, *in vitro* 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 *in vitro* data, Evrysdi may increase plasma concentrations of drugs eliminated via MATE1 or MATE2-K. The clinical relevance of the co-administration with MATE1/2-K substrates is unknown.

Based on in vitro data, risdiplam may increase plasma concentrations of medicinal products eliminated via MATE1 or MATE2-K, such as metformin. If coadministration cannot be avoided, drug-related toxicities should be monitored and dosage reduction of the co-administered medicinal product should be considered if needed.

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.

## 3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

## 3.1 PHARMACODYNAMIC PROPERTIES

### 3.1.1 Mechanism of Action

Risdiplam is a survival of motor neuron 2 (SMN2) pre-mRNA splicing modifier designed to treat SMA 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 corrects the splicing of SMN2 to shift the balance from exon 7 exclusion to exon 7 inclusion into the mRNA transcript leading to an increased production in functional and stable SMN protein. Thus, risdiplam treats SMA by increasing and sustaining functional SMN protein levels.

Risdiplam distributes evenly to all parts of the body, including the central nervous system (CNS) by crossing the blood brain barrier, and thereby leading to SMN protein increase in the CNS and throughout the body. Concentrations of risdiplam in plasma and SMN protein in blood reflect its distribution and pharmacodynamic effects in tissues such as brain and muscle.

In FIREFISH, SUNFISH and JEWELFISH clinical trials for infantile-onset SMA and later-onset SMA patients, 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 at least 24 months (see section *3.1.2 Clinical / Efficacy Studies*).

**Cardiac Electrophysiology**

The effect of risdiplam on the QTc interval was evaluated in a study in 47 healthy adult subjects. At the therapeutic exposure, risdiplam did not prolong the QTc interval.

### 3.1.2 Clinical / Efficacy Studies

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, and supported by additional data from the JEWELFISH study. The efficacy of Evrysdi for the treatment of pre-symptomatic SMA patients was evaluated in the RAINBOWFISH study. The overall findings of these studies support the effectiveness of Evrysdi for SMA patients.

***Infantile-onset SMA***

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 *section 2.2 Dosing and Administration*). 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 therapeutic dose. The median age of onset of clinical signs and symptom was 1.5 months (range: 0.9 to 3.0 months). The median age at enrolment 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. At baseline the median CHOP-INTEND score was 23 (range: 8 to 37), and the median HINE-2 score was 1 (range: 0 to 5). The baseline demographics and disease characteristics of those enrolled in Part 1 were comparable to those in Part 2.

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, 90% CI: 17.8%, 43.1%, p <0.0001) achieved this milestone.

The key efficacy endpoints of Evrysdi treated patients in FIREFISH Part 1 and Part 2 are shown in Table 5, and displayed in Figure 1 and Figure 2.

**Table 5 Summary of Key Efficacy Endpoints at Month 12 and Month 24 (FIREFISH Part 1 and Part 2)**

| Efficacy Endpoints | Month 12 | Month 24 |
|---|---|---|
| | **Proportion of Patients** (90% CI) | |
| Motor Function and Development Milestones | **N = 58[a]** | |
| BSID-III: sitting without support for at least 5 seconds | 32.8% (22.6%, 44.3%) | 60.3% (48.7%, 71.2%) |
| CHOP-INTEND: score of 40 or higher | 56.9% (45.3%, 68.0%) | 74.1% (63.0%, 83.3%) |
| CHOP-INTEND: increase of ≥4 points from baseline | 89.7% (80.6%, 95.4%) | 87.9% (78.5%, 94.2%) |
| HINE-2: motor milestone responders[b] | 77.6% (66.7%, 86.2%) | 82.8% (72.5%, 90.3%) |
| Feeding | | |
| Ability to feed orally[c] | 84.5% (74.5%, 91.7%) | 82.8% (72.5%, 90.3%) |
| Healthcare Utilization | | |
| No hospitalizations[d] | 48.3% (36.9%, 59.8%) | 34.5% (24.2%, 46.0%) |
| Survival and Event-Free Survival | **N=62[a]** | |
| Event-free survival[e] | 87.1% (78.1%, 92.6%) | 83.8% (74.3%, 90.1%) |
| Alive | 91.9% (83.9%, 96.1%) | 90.3% (81.9%, 94.9%) |

Abbreviations: BSID-III: Bayley Scales of Infant and Toddler Development – Third Edition; CHOP-INTEND=Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2=Module 2 of the Hammersmith Infant Neurological Examination.

[a] For survival and ventilation-free survival, data were pooled from all patients who received any dose of risdiplam in Part 1 and Part 2 (n=62). For the motor function and development milestone, feeding, and healthcare utilization efficacy endpoints, data were pooled from all patients who received the therapeutic dose of risdiplam (all patients in Part 2 and those in the high-dose cohort of Part 1; n=58).

[b] HINE-2 responder definition: ≥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] Includes patients who were fed exclusively orally (41 patients at Months 12 and 24) and those who were fed orally in combination with a feeding tube (8 patients at Month 12 and 7 patients at Month 24).

[d] Hospitalizations include all hospital admissions which spanned at least two days.

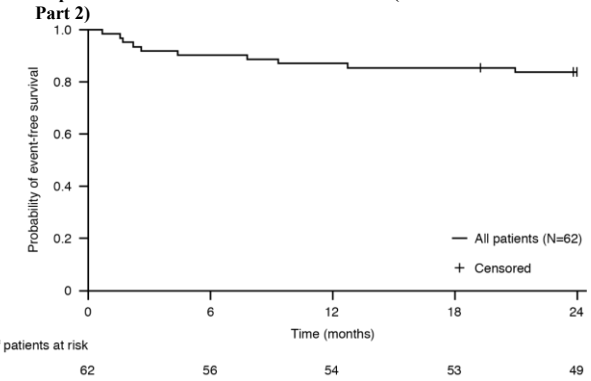
[e] An event is meeting the endpoint of permanent ventilation defined as tracheostomy or ≥16 hours of non-invasive ventilation per day or intubation for > 21 consecutive days in the absence of, or following the resolution of, an acute reversible event. Four patients met the endpoint of permanent ventilation before Month 24. These 4 patients achieved an increase of at least 4 points in their CHOP-INTEND score from baseline.

At Month 24, 40% (23/58) of patients who received the therapeutic dose achieved sitting without support for 30 seconds (BSID-III, Item 26). In addition, patients continued to achieve additional motor milestones as measured by the HINE-2 at Month 24; 78% of patients were able to roll (31% of patients could roll to the side, 7% could roll from prone to supine and 40% could roll from supine to prone), and 28% of patients achieved a standing measure (16% supporting weight and 12% standing with support).

The proportion of patients alive without permanent ventilation (event-free survival) was 84% for all patients at Month 24, see Figure 1. Six infants died (4 within the first 3 months following study enrolment) and one additional patient withdrew from treatment and died 3.5 months later. Four patients required permanent ventilation by Month 24.

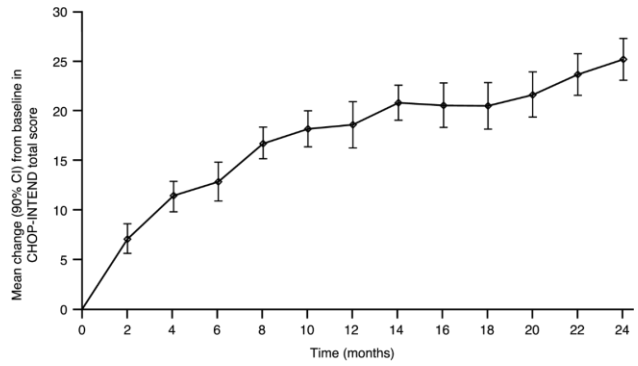
These results indicate a clinically meaningful deviation from the natural history of untreated infantile-onset SMA. Untreated patients with infantile-onset SMA would never be able to sit without support and only 25% would be expected to survive without permanent ventilation beyond 14 months of age.

**Figure 1 Kaplan-Meier Plot of Event-Free Survival (FIREFISH Part 1 and Part 2)**




+ Censored: two patients were censored because they attended the Month 24 visit early, 1 one patient was censored after discontinuing treatment and died 3.5 months later

**Figure 2 Mean change from baseline in CHOP-INTEND Total Score (FIREFISH Part 1 and Part 2)**




***Later Onset SMA***

Study BP39055 (SUNFISH), is a 2-part, multicenter trial to investigate the efficacy, safety, PK and PD of Evrysdi in SMA Type 2 or Type 3 patients between 2-25 years of age. Part 1 was the 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*

SUNFISH 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 section *2.2 Dosage and Administration*) 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% Caucasian and 19% Asian. At baseline, 67% of patients had scoliosis (32% of patients 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).

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 6, Figure 3, and Figure 4.

**Table 6 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<br>LS Mean (95%, CI) | 1.36 (0.61, 2.11) | -0.19 (-1.22, 0.84) |
| Difference from Placebo<br>Estimate (95% CI)<br>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)<br>Adjusted (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<br>LS Mean (95% CI) | 1.61 (1.00, 2.22) | 0.02 (-0.83, 0.87) |
| Difference from Placebo<br>Estimate (95% CI) adjusted (unadjusted) p-value[2,4] | 1.59 (0.55, 2.62) 0.0469 (0.0028) | |

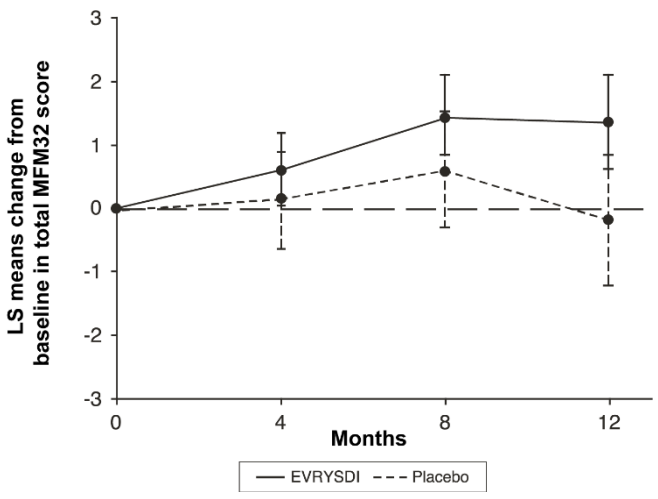
LS=least squares

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 analysed using a mixed model repeated measure with baseline total score, treatment, visit, age group, treatment-by-visit and baseline-by-visit.
3. Data analysed 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 demonstrated significant improvements in motor function assessed by the MFM32 (1.55 points mean difference; p = 0.0156) after 12 months of treatment. Patients 2-5 years old treated with Evrysdi demonstrated the greatest improvement on MFM32 compared to placebo control (≥3 points increase: 78.1% vs 52.9%). Patients ≥18 years old treated with Evrysdi achieved stabilization of disease (change from baseline MFM32 total score ≥ 0 point(s): 57.1% vs. 37.5%). 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.

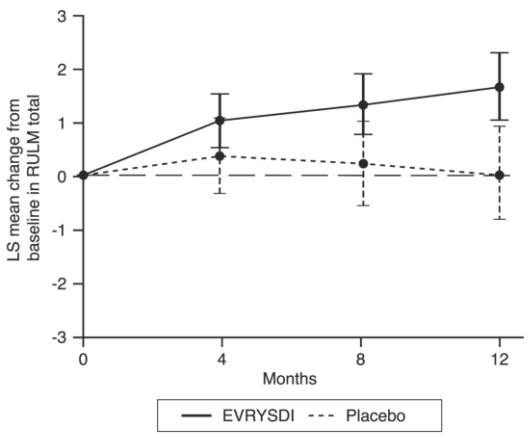
The study also met a secondary independent motor function outcome, RULM. On the RULM, statistically significant and clinically meaningful improvements in motor function were observed after 12 months of treatment compared to baseline. The patients 2-5 years old treated with Evrysdi demonstrated the greatest improvement on the RULM (3.41 points [95% CI: 1.55, 5.26]) and improvement was also observed in the patients ≥18 years old (1.74 points [95% CI: -1.06, 4.53])

**Figure 3 Mean Change from Baseline in Total MFM32 Score Over 12 months in SUNFISH Part 2[1]**




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

**Figure 4 Mean Change from Baseline in Total RULM Score Over 12 months in SUNFISH Part 2[1]**




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

Upon completion of 12 months of treatment, 117 patients continued to receive Evrysdi. At the time of the 24 month analysis, these patients who were treated with Evrysdi for 24 months overall experienced maintenance of improvement in motor function between month 12 and month 24. The mean change from baseline for MFM32 was 1.83 (95% CI: 0.74, 2.92) and for RULM was 2.79 (95% CI: 1.94, 3.64) at month 24.

*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 at the therapeutic dose (the dose selected for Part 2), 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]).

In an exploratory analysis, the motor function assessed by MFM was compared between SUNFISH Part 1 and a natural history cohort (weighted based on key prognostic factors). The MFM total change from baseline after 1 year and 2 years was greater in patients receiving Evrysdi compared to the natural history cohort (after 1 year: 2.7 point difference; p< 0.0001; after two years; 4.0 point difference; p< 0.0001). The natural history cohort experienced a decline in motor function as expected based on the natural progression of SMA (after 1 year: -0.6 mean change; after 2 years: -2.0 mean change).

***Pre-symptomatic SMA***

Study BN40703 (RAINBOWFISH) is an open-label, single-arm, multicenter clinical study to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of Evrysdi in infants from birth 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 [intent-to-treat(ITT) population] who had been treated with Evrysdi. The median age of these patients at first dose was 25 days (range: 16 to 41 days), 62% were female, 85% were Caucasian. Eight patients, 13 patients, and 5 patients had 2, 3, and ≥4 copies of the *SMN2* gene, respectively. At baseline the median CHOP-INTEND score was 51.5 (range: 35.0 to 62.0), the median HINE-2 score was 2.5 (range: 0 to 6.0), and the median ulnar nerve compound muscle action potential (CMAP) amplitude was 3.6 mV (range: 0.5 to 6.7 mV).

The primary efficacy population (N=5) included patients with 2 *SMN2* copies and a baseline CMAP amplitude ≥1.5mV. In these patients, the median CHOP-INTEND score was 48.0 (range: 36.0 to 52.0), the median HINE-2 score was 2.0 (range 1.0 to 3.0), and the median CMAP amplitude was 2.6mV (range: 1.6 to 3.8 mV) at baseline.

The primary endpoint was the proportion of patients in the primary efficacy population with the ability to sit without support for at least 5 second (BSID-III gross motor scale, Item 22) at Month 12; a statistically significant and clinically meaningful proportion of patients achieved this milestone compared to the predefined performance criterion of 5%.

The key efficacy endpoints of Evrysdi treated patients are shown in Table 7 and 8, and Figure 5.

**Table 7 Sitting Ability as defined by BSID-III Item 22 for Pre-symptomatic Patients at Month 12**

| Efficacy Endpoint | Population | | |
|---|---|---|---|
| | Primary Efficacy (N=5) | Patients with 2 SMN2 copies[a] (N=8) | ITT (N=26) |
| Proportion of patients sitting without support for at least 5 seconds (BSID-III, Item 22); (90% CI) | 80% (34.3%, 99.0%) p < 0.0001[b] | 87.5% (52.9%, 99.4%) | 96.2% (83.0%, 99.8%) |

Abbreviations: BSID-III = Bayley Scales of Infant and Toddler Development – Third Edition; CI=Confidence Interval; ITT=Intent-to-treat.

[a] Patients with 2 *SMN2* copies had a median CMAP amplitude of 2.0 (range 0.5 - 3.8) at baseline.

[b] p-value is based on a one-sided exact binomial test. The result is compared to a threshold of 5%.

Additionally, 80% (4/5) of the primary efficacy population, 87.5% (7/8) of patients with 2 *SMN2* copies, and 80.8% (21/26) of patients in the ITT population achieved sitting without support for 30 seconds (BSID-III, Item 26).

Patients in the ITT population also achieved motor milestones as measured by the HINE-2 at Month 12 (N=25). In this population 96.0% of patients could sit [1 patient (1/8 patients with 2 *SMN2* copies) achieved stable sit and 23 patients (6/8, 13/13, 4/4 of patients with 2, 3, and ≥4 *SMN2* copies, respectively) could pivot/rotate]. In addition, 84% of patients could stand; 32% (N=8) patients could stand with support (3/8, 3/13 and 2/4 patients with 2, 3, and ≥4 *SMN2* copies, respectively) and 52%

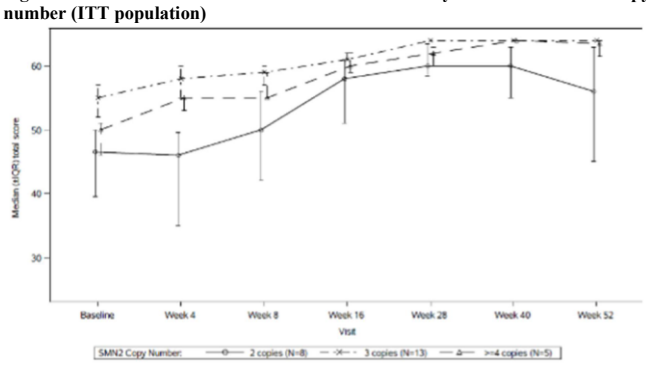
(N=13) patients could stand unaided (1/8, 10/13 and 2/4 of patients with 2, 3, and ≥4 *SMN2* copies, respectively). Furthermore, 72% of patients could bounce, cruise or walk; 8% (N=2) patients could bounce (2/8 patients with 2 *SMN2* copies), 16% (N=4) could cruise (3/13 and 1/4 patients with 3 and ≥4 *SMN2* copies, respectively) and 48% (N=12) could walk independently (1/8, 9/13 and 2/4 patients with 2, 3, and ≥4 *SMN2* copies, respectively). Seven patients were not tested for walking at Month 12.

**Table 8 Summary of Key Efficacy Endpoints for Pre-symptomatic Patients at Month 12**

| Efficacy Endpoints | ITT population (N=26) |
|---|---|
| Motor Function | |
| Proportion of patients who achieve a Total score of 50 or higher in the CHOP-INTEND (90% CI) | 92%[a] (76.9%, 98.6%) |
| Proportion of patients who achieve a Total score of 60 or higher in the CHOP-INTEND (90% CI) | 80%[a] (62.5%, 91.8%) |
| Feeding | |
| Proportion of patients with the ability to feed orally; (90% CI) | 96.2%[b] (83.0%, 99.8%) |
| Healthcare Utilization | |
| Proportion of patients with no hospitalizations[c]; (90% CI) | 92.3% (77.7%, 98.6%) |
| Event-Free Survival[d] Proportion of patients with Event-Free Survival; (90% CI) | 100% (100%, 100%) |

Abbreviations: CHOP-INTEND=Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI=Confidence Interval; ITT = Intent-to-treat
[a] Based on N=25
[b] One patient was not assessed.
[c] Hospitalizations include all hospital admissions which spanned at least two days, and which were not due to study requirements.
d An event refers to death or permanent ventilation; permanent ventilation is 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.

**Figure 5 Median Total CHOP-INTEND Scores by Visit and *SMN2* copy number (ITT population)**




Abbreviations: IQR – Interquartile range; SMN2=Survival of Motor Neuron

***Use in Patients Previously Treated with Other SMA Modifying Therapies***
Study BP39054 (JEWELFISH) is a single arm, open-label study to investigate the safety, tolerability, PK and PD of Evrysdi in patients with infantile-onset and later-onset SMA between 6 months and 60 years of age, who were previously treated with other SMA-modifying therapies (including nusinersen and onasemnogene abeparvovec). Of the 174 patients enrolled, 76 patients previously received treatment with nusinersen (9 patients with Type 1 SMA, 43 with Type 2 SMA and 24 with Type 3 SMA) and 14 patients previously received treatment with onasemnogene abeparvovec (4 patients with Type 1 SMA and 10 with Type 2 SMA). The median age of patients at the start of Evrysdi treatment was 14 years (range 1-60 years). At baseline, 83% of patients of the 168 patients 2-60 years had scoliosis (39% of patients had severe scoliosis) and 63% of patients had a Hammersmith Functional Motor Scale Expanded (HFMSE) score <10 points. The study also included 15 ambulant patients (2-46 years of age).

Patients had a greater than 2-fold median increase in SMN protein levels in blood compared to baseline after 4 weeks of Evrysdi treatment. The increase in SMN protein was maintained throughout the treatment period of at least 2 years.

Exploratory efficacy was assessed with age appropriate motor function measures including MFM-32 and RULM scales for patients 2-60 years of age, BSID-III and HINE-2 for patients less than 2 years of age and the Six-Minute Walk Test (6MWT) in ambulant patients ≥ 6 years of age. At the primary analysis scheduled at month 24 of treatment, patients 2-60 years of age showed overall stabilization in motor function in MFM-32 and RULM (n=137, and n=133, respectively). Patients less than 2 years (n=6) maintained or gained motor milestones such as head control, rolling and sitting independently. The 6MWT results showed a mean improvement of 30.88 meters (95% CI: -5.54, 67.29, n=8). All ambulatory patients retained their ability to walk. The safety data in JEWELFISH are consistent with the known safety profile of treatment naïve SMA patients receiving Evrysdi.

### 3.1.3 Immunogenicity
Not applicable

## 3.2 PHARMACOKINETIC PROPERTIES
Pharmacokinetic parameters for Evrysdi have been characterized in healthy adult subjects and in patients with SMA.

After administration of Evrysdi as an oral solution, PK of risdiplam were approximately linear between 0.6 and 18 mg. Risdiplam's PK 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 PK. The pharmacokinetics of the tablet (swallowed or dispersed in water) were bioequivalent to the oral solution.

The estimated exposure (mean $AUC_{0\text{-}24h}$) for infantile-onset SMA patients (age 2-7 months at enrollment) at the therapeutic dose of 0.2 mg/kg once daily was 1930 ng.h/mL. For pre-symptomatic infants (age 16 days to <2 months) in the RAINBOWFISH study, the estimated exposure is 2020 ng.h/mL at 0.15 mg/kg after 2 weeks once daily administration. The estimated exposure for later-onset SMA patients (2-25 years old at enrollment) in the SUNFISH study (Part 2) at the therapeutic dose (0.25 mg/kg once daily for patients with a body weight <20 kg; 5 mg once daily for patients with a body weight ≥20 kg) was 2070 ng.h/mL. The observed maximum concentration (mean $C_{max}$) was 194 ng/mL at 0.2 mg/kg in FIREFISH and 120 ng/mL in SUNFISH Part 2, and the estimated maximum concentration at 0.15 mg/kg in RAINBOWFISH is 111 ng/mL.

### 3.2.1 Absorption
Risdiplam was rapidly absorbed in the fasted state with a plasma $t_{max}$ ranging from 1 to 5 hours after oral administration of the solution, the tablet or the dispersed tablet. Based on data in 47 healthy subjects, food (high-fat, high calorie breakfast) had no relevant effect on the exposure of risdiplam. In the clinical studies, risdiplam was administered with a morning meal or after breastfeeding.

### 3.2.2 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%.

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

Co-administration of 200 mg itraconazole twice daily, a strong CYP3A inhibitor, with a single oral dose of 6 mg risdiplam showed no clinically relevant effect on the PK of risdiplam (11% increase in AUC, 9% decrease in $C_{max}$).

### 3.2.4 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.

Risdiplam is not a substrate of human multidrug resistance protein 1 (MDR1).

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.

### 3.2.5 Pharmacokinetics in Special Populations
***Pediatric Population***
Body weight and age were identified as covariates in the population PK analysis. The dose is therefore adjusted based on age (below and above 2 months and 2 years) and body weight (up to 20 kg) to obtain similar exposure across the age and body weight range. No data are available in patients less than 16 days of age. Dosing regimen in patients < 2 months of age was determined using pharmacokinetic modelling and simulation with PK data collected from pediatric patients aged 16 days and older.

***Geriatric Population***
No dedicated studies have been conducted to investigate the PK of Evrysdi in patients with SMA above 60 years of age. Patients with SMA up to 60 years of age were included in the JEWELFISH study. Subjects without SMA up to 69 years of age were included in clinical PK studies, which indicates that no dose adjustment is required for patients up to 69 years of age.

***Renal impairment***
No studies have been conducted to investigate the PK of risdiplam in patients with renal impairment. Elimination of risdiplam as unchanged entity via renal excretion is minor (8%).

***Hepatic impairment***
Mild and moderate hepatic impairment had no impact on the PK of risdiplam. After administration of 5 mg risdiplam, the mean ratios for $C_{max}$ and AUC were 0.95 and 0.80 in mild (n=8) and 1.20 and 1.08 in moderate hepatic impaired subjects (n=8) versus matched healthy controls (n=10). The safety and PK in patients with severe hepatic impairment have not been studied.

***Ethnicity***
The PK of risdiplam do not differ in Japanese and Caucasian subjects.

## 3.3 NONCLINICAL SAFETY
### 3.3.1 Carcinogenicity
A 2-year carcinogenicity study in rats was conducted with daily oral doses of 0.3, 1, and 3 mg/kg of risdiplam. Risdiplam did not induce tumors at the low and mid-dose, where observed exposures in rats were equivalent to those in humans at the maximum recommended human dose (MRHD) of 5mg. Statistically significant increases in tumors of the preputial gland in male rats and clitoral gland in female rats were seen at the high dose of 4 times the exposure of the MRHD. As these are both rodent-specific organs, these findings have no human relevance. A study using rasH2 transgenic mice with 6 months duration of treatment did not generate any evidence for a tumorigenic potential.

### 3.3.2 Genotoxicity
Risdiplam is not mutagenic in a bacterial reverse mutation assay. In mammalian cells *in vitro* and in bone marrow of rats, risdiplam increases the frequency of micronucleated cells. 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 of approximately 1.5-fold 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. These effects also manifest in other tissues with high cell turnover with changes on the skin, the gastrointestinal (GI) tract, in male germ cells, in embryonal toxicity, and in the bone marrow. Risdiplam does not possess a potential to damage DNA directly.

### 3.3.3 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/aspermia 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 reached at the therapeutic dose of risdiplam in patients. However, there was no impairment on male fertility seen in a respective study in 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 reversible. No effects were seen on female reproductive organs in rats and monkeys after treatment with risdiplam.

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

In a pre- and post-natal study in rats treated daily with risdiplam, risdiplam caused a slight delay in gestation length. No adverse effects were recorded on the survival, growth, functional (behavioral or reproductive) performance of the offspring. 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.

### 3.3.5 Other
**Effect on retinal structure**
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. Upon cessation of treatment, the effects on the retinogram were partially reversible but the photoreceptor degeneration did not reverse. The effects were monitored by optical coherence tomography (OCT) and in the electroretinography (ERG). 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 in excess of 2 times the 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. Such findings have not been observed in clinical trials in SMA patients with regular ophthalmological monitoring (including SD OCT and visual function assessment).

**Effect on epithelial tissues**
Effects on skin, larynx and eyelid histology and the GI tract were evident in rats and monkeys treated with risdiplam. Changes started to be seen at high doses with treatment of 2 weeks and longer. With chronic treatment for 39 weeks in monkeys the NOAEL was at an exposure in excess of 2-times the average exposure in humans at the therapeutic dose. Skin epithelial effects as observed in animal studies have not been observed in clinical trials in SMA patients.

**Effect on hematological parameters**
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 in excess of 15-times the average exposure in humans at the therapeutic dose. With treatment of rats for 4 weeks, such effects were not seen up to the highest dose with an exposure of approximately 7-times the average exposure in humans at the therapeutic dose while 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 approximately 3.5 times higher than 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 1.5 fold the average exposure in humans at the therapeutic dose. Hematological parameters remained unchanged during treatment with Evrysdi in clinical trials in SMA patients.

**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. 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.

# 4. PHARMACEUTICAL PARTICULARS
## 4.1 STORAGE
**Storage**
*As registered locally.*

***Evrysdi Powder for Oral Solution:***
Keep in the original amber bottle.

Powder: Do not store above 25°C.

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.

***Evrysdi Film-Coated Tablets***
Keep in the original package to protect from moisture.

Do not store above 30°C.

**Shelf life**
*As registered locally.*

***Evrysdi Powder for Oral Solution:***
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.

***Evrysdi Film-coated Tablets:***
As registered locally.

## 4.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL
***Evrysdi Powder for Oral Solution:***

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

Evrysdi powder must be constituted to the oral solution by a HCP prior to being dispensed.

Caution should be exercised in the handling of Evrysdi powder for oral solution (see section *2.4 Warning 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 9 Selecting the Oral Syringe for the Prescribed Daily Dose of Evrysdi**

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

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 Evrysdi oral solution (0.75 mg/mL)*
Refer to section *2.2 Dosage and Administration* for the proper dosing regimen instructions.

*For detailed instructions on constitution and administration please refer to the Instructions for Constitution and Instructions for Use.* 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.

***Preparation of the Dispersion of Evrysdi Film-coated Tablets***
It is recommended that an HCP discuss with the patient or caregiver how to prepare the prescribed daily dose prior to administration of the first dose.

Refer to *Section 2.2 Dosage and Administration* for the proper dosing regimen instructions.

*For detailed instructions on the dispersion and administration of Evrysdi film-coated tablets in non-chlorinated drinking water (e.g. bottled water), please refer to the Instructions for Use.*

The Evrysdi film-coated tablet should be swallowed whole with water or dispersed in a small amount of room temperature non-chlorinated drinking water (e.g. bottled water) (see section 4.2 Special Instruction for Use, Handling and Disposal). Do not chew, cut or crush the tablets.

If Evrysdi film-coated tablet is dispersed in non-chlorinated drinking water (e.g. bottled water), take it immediately. Evrysdi film-coated tablets should not be dispersed in any liquid other than non-chlorinated drinking water (e.g. bottled water). Discard the prepared dispersion if it is not used within 10 minutes of adding water. Do not expose the prepared dispersion to sunlight.

If prepared dispersion of Evrysdi spills or gets on the skin, the area should be washed with soap and water.

Evrysdi film-coated tablets should not be used for administration via nasogastric or gastrostomy tube. If administration through a nasogastric or gastrostomy tube is required, Evrysdi powder for oral solution should be used.

**Disposal of unused/expired medicines**
The release of pharmaceuticals in the environment must be minimised. Evrysdi film-coated tablets must not be disposed of via wastewater.

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

## 4.3 PACKS
***Evrysdi Powder for Oral Solution:***
Bottle containing powder for oral solution 1

***Evrysdi Film-coated Tablets:***
OPA/Aluminium/PVC-Aluminium blister strips containing 7 film-coated tablets. Each carton contains 28 film-coated tablets (1 carton with 4 blister strips).

**Medicine: keep out of reach of children**

Current at February 2026

Roche F. Hoffmann-La Roche Ltd, Basel, Switzerland

## Instructions For Constitution (0.75 mg/mL)

# EVRYSDI®

Risdiplam

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Instructions for Constitution
**(FOR HEALTHCARE PROFESSIONALS ONLY)**

**Each Evrysdi carton contains (See figure A):**
1. 1 Cap
2. 1 Evrysdi bottle
3. 1 Oral syringe 12 mL (in a pouch)
4. 2 Oral syringes 6 mL (in pouches)
5. 2 Oral syringes 1mL (in pouches)
6. 1 Press-in bottle adapter

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 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 Evrysdi**
- 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.

**Constitution**

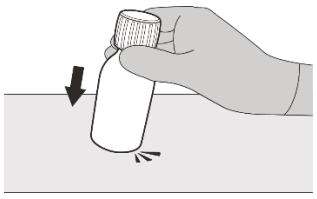


Figure B

**Step 1**
Gently tap the bottom of the bottle to loosen the powder (see Figure B).

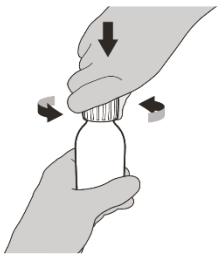


Figure C

**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.

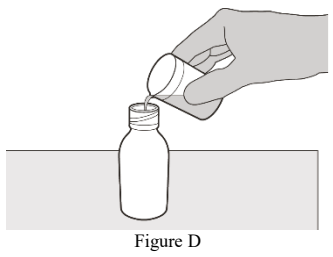


Figure D

**Step 3**
Carefully pour 79 mL of Purified Water or Water for Injection (WFI) into the medicine bottle (see Figure D).

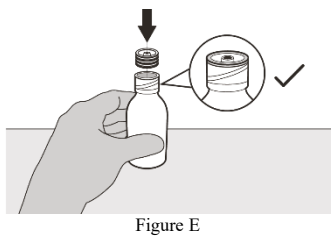


Figure E

**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).

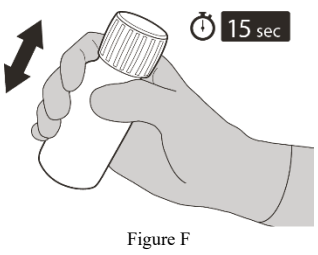



Figure F

**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.

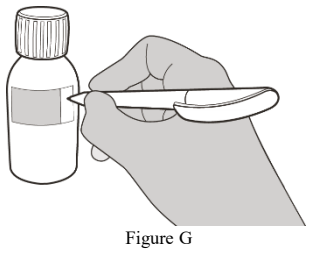


Figure G

**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 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) and carton.

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

## Instructions For Use – Administration (0.75 mg/mL)

# EVRYSDI®

Risdiplam

---

**Instructions for 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.

**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 the oral syringes provided in the pack 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 daily dose of Evrysdi**" 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 Evrysdi and then contact your healthcare professional.
- **Do not** use Evrysdi 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 Evrysdi into food or liquids (e.g. milk or formula milk).
- **Do not** use Evrysdi if the bottle or oral syringes are damaged.
- **Avoid** getting Evrysdi on your skin. If Evrysdi gets on your 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 your 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 your prescribed daily dose. **Do not mix** Evrysdi 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 1 mL (in pouches)

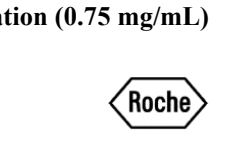
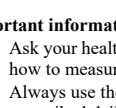


Figure A

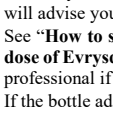
**How to store Evrysdi**
Please see section *4.1 Storage* of the Package Leaflet for full information.

**A) Preparing and withdrawing your daily dose**
How to select the correct oral syringe to use for your prescribed daily dose of Evrysdi

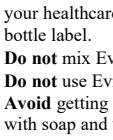
- If your prescribed daily dose of Evrysdi is between 0.3 mL and 1 mL, use a 1 mL oral syringe (yellow label). Ask your healthcare professional about rounding your or your child's daily dose to the nearest 0.01 mL.




- If your prescribed daily dose of Evrysdi is between 1 mL and 6 mL, use a 6 mL oral syringe (grey label). Ask your healthcare professional about rounding your or your child's daily dose to the nearest 0.1 mL.




- If your prescribed daily dose of Evrysdi is 6.2 mL or higher, use a 12 mL oral syringe (brown label). Ask your healthcare professional about rounding your or your child's daily dose to the nearest 0.2 mL.




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

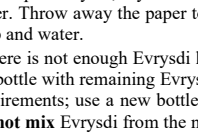


Figure B

**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.

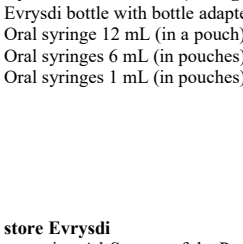


Figure C

**Step A2**
Push the plunger of the oral syringe all the way down to remove any air in the oral syringe (See Figure C).

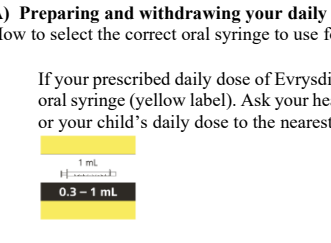


Figure D

**Step A3**
Keeping the bottle in an upright position, insert the syringe tip into the bottle adapter (See Figure D).

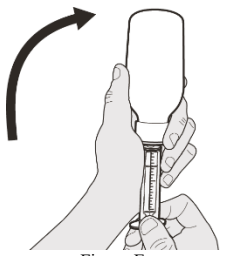


Figure E

**Step A4**
Carefully turn the bottle upside down with the syringe tip firmly inserted into the bottle adapter (See Figure E).

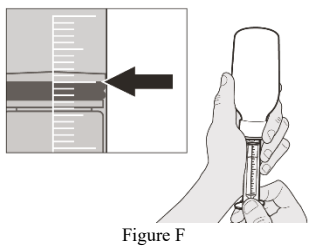


Figure F

**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 daily dose (See Figure F).

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

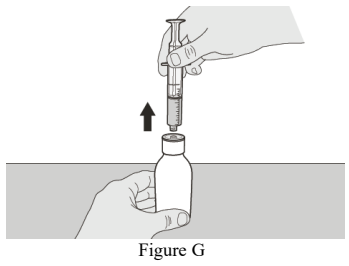


Figure G

**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).

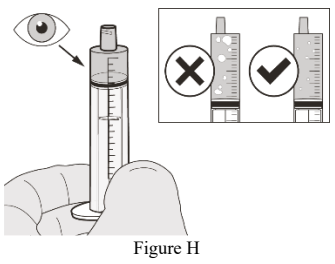


Figure H

**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.

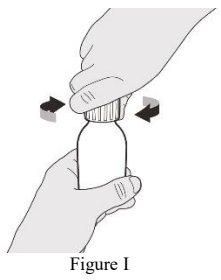


Figure I

**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.

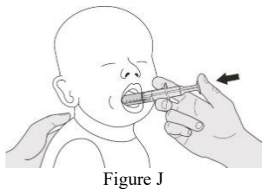


Figure J

**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.**

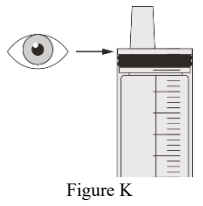


Figure K

**Step B2**
Check that there is no medicine left in the oral syringe (See Figure K).

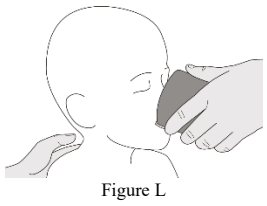


Figure L

**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.

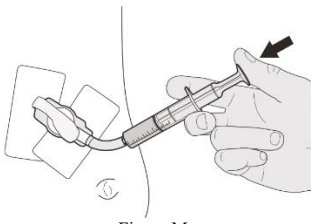


Figure M

**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).

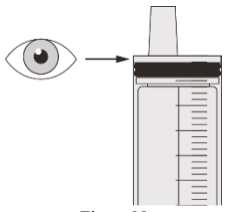


Figure N

**Step C2**
Check that there is no medicine left in the oral syringe (See Figure N).

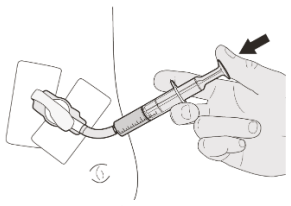


Figure O

**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.

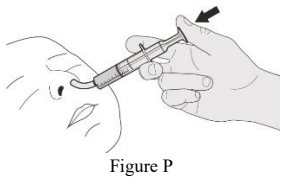


Figure P

**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).

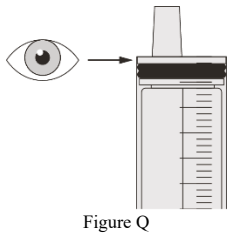


Figure Q

**Step D2**
Check that there is no medicine left in the oral syringe (See Figure Q).

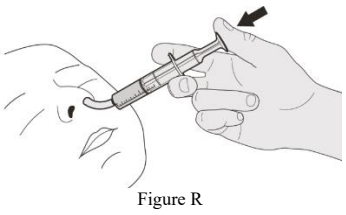


Figure R

**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**

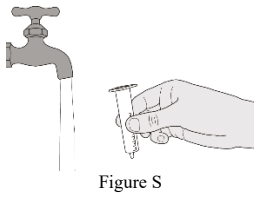


Figure S

**Step E1**
Remove the plunger from the oral syringe.
Rinse the oral syringe barrel well under clean water (See Figure S).

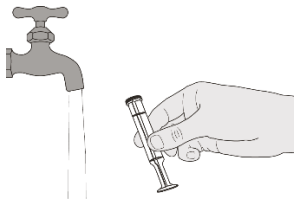


Figure T

**Step E2**
Rinse the plunger well under clean water (See Figure T).

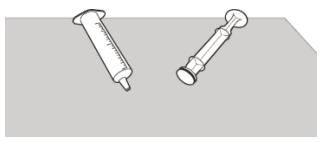


Figure U

**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.

## Instructions For Use – Administration

# EVRYSDI®

(risdiplam) film-coated tablets

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This Instructions for Use contains information on how to prepare and take Evrysdi.

- The information in this Instructions for Use is for taking or giving this medicine – but here we just say 'take'.

**Before you start**
**Read this Instructions for Use** before taking Evrysdi film-coated tablets for the first time and each time you get a refill. There may be new information.

**Evrysdi film-coated tablets can be swallowed whole or mixed with a small amount of room temperature non-chlorinated drinking water (e.g. bottled water) and taken by mouth.**

Do not give Evrysdi film-coated tablets with a nasogastric tube (NG-tube) or gastrostomy tube (G-tube).

**Important information**

- Your doctor, pharmacist, or nurse will show you how to prepare and take Evrysdi tablets. Always take Evrysdi tablets exactly as your healthcare provider tells you.
- Do not take or give this medicine until you have been shown how to properly prepare and take Evrysdi.
- Wash your hands before and after preparing or taking Evrysdi.
- Check the expiry date and check the product for damage before use. Do not use if expired or damaged.
- Do not get the Evrysdi tablet mixture on your skin or in your eyes. If the Evrysdi tablet mixture gets on your skin, wash the area with soap and water. If the tablet mixture gets in your eyes, rinse your eyes with water.
- Keep the Evrysdi tablet mixture out of sunlight.
- If you spill the Evrysdi tablet mixture, dry the area with a dry paper towel and then clean with soap and water. Throw away the paper towel in the rubbish and wash your hands with soap and water.

**How to take Evrysdi tablets**

- If you are taking Evrysdi tablets, the daily dose is 1 tablet.
- Take the tablet whole with water or as a liquid by mixing 1 tablet in at least 1 teaspoon (5 ml) of room temperature non-chlorinated drinking water (e.g. bottled water).
- Do not chew, cut, or crush the tablet.
- Do not mix Evrysdi with any liquids other than non-chlorinated drinking water (e.g. bottled water).
- Do not take Evrysdi tablet mixture if it has been more than 10 minutes since adding water to the tablet. Throw the mixture away according to your local requirements and make a new dose.
- Do not take an extra dose if you are sick (vomit) at any time after taking Evrysdi.

**Get ready to take an Evrysdi tablet**

**Step 1**
Wash your hands (Figure A).

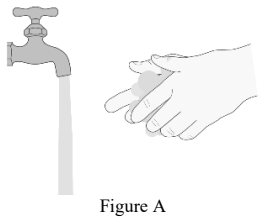

Figure A

**Step 2**
Take our 1 Evrysdi tablet from the blister (Figure B).


Figure B

**Option A: Swallow the Evrysdi tablet whole**

**Step A1**

Swallow the tablet whole with some water.

**Do not** chew, cut, or crush the tablet.

**Do not** swallow with any liquids other than water.

**Step A2**

Wash your hands with soap and water.

**Option B: Take Evrysdi tablet mixed in non-chlorinated drinking water (e.g. bottled water)**

**What is needed to mix** Evyrsdi **with non-chlorinated drinking water (e.g. bottled water:**

- 1 Evrysdi tablet
- a small, clean empty cup
- at least 1 teaspoon (5ml) of room temperature non-chlorinated drinking water (e.g. bottled water) for mixing
- at least 1 tablespoon (15ml) of non-chlorinated drinking water (e.g. bottled water) for rinsing

**Step B1**
Put at least 1 teaspoon (5ml) of non-chlorinated drinking water (e.g. bottled water) in a cup – and add 1 tablet.

- **Do not** use any liquids other than non-chlorinated drinking water (e.g. bottled water),
- Keep the mixture out of sunlight.


Figure C

**Step B2**
Gently swirl the cup until it is fully mixed – this can take up to 3 minutes (Figure C).

**Step B3**
Drink immediately within 10 minutes of adding non-chlorinated drinking water (e.g. bottled water) to the tablet (Figure D).

Figure D

**Step B4**
Refill the cup with at least 1 tablespoon (15ml) of non-chlorinated drinking water (e.g. bottled water) and swirl to get any medicine left in the cup (Figure E).

Figure E

**Step B5**
Drink immediately (Figure F).

Figure F

**Step B6**
Wash your hands with soap and water.

**Storing Evrysdi**

- Evrysdi film-coated tablets should be stored in accordance with the locally registered temperature storage statement.
- Keep in the original package to protect from moisture.
- Keep Evrysdi and all medicines out of the sight and reach of children.