EVRYSDI®
Risdiplam

Information as set forth in this label only applies to Evrysdi

1. DESCRIPTION
1.1 THERAPEUTIC/PHARMACOLOGIC CLASS OF DRUG

Pharmacotherapeutic group: Other drugs for disorders of the musculoskeletal system.
ATC code: M09AX10.

1.2 TYPE OF DOSAGE FORM

Powder for oral solution.

1.3 ROUTE OF ADMINISTRATION

Oral or enteral.

1.4 STERILE/RADIOACTIVE STATEMENT

Not applicable.

1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: risdiplam.

Excipients: mannitol, isomalt, strawberry flavor, tartaric acid, sodium benzoate, polyethylene glycol, sucralose, ascorbic acid, and disodium edetate dehydrate.

Evrysdi is supplied as a powder in an amber glass bottle. Each bottle is filled with 2.0 g of powder that 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*).

2. CLINICAL PARTICULARS
2.1 THERAPEUTIC INDICATION(S)

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

2.2 DOSAGE AND ADMINISTRATION

Evrysdi oral solution must be constituted by a healthcare provider prior to being dispensed.

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

Evrysdi is taken orally once daily using the oral syringe provided, at approximately the same time each day.

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

Table 1 Dosing Regimen by Age and Body Weight

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

Dose changes must be made under the supervision of a healthcare provider. Treatment with a daily dose above 5 mg has not been studied. No data are available in infants below 2 months of age.

Method of Administration
Use the reusable oral syringe provided to deliver the daily dose of Evrysdi. It is recommended a healthcare provider 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 Instructions for Use, Handling and Disposal*).

Evrysdi is taken orally once a day after a meal at approximately the same day each day, using the reusable oral syringe provided. In infants who are breastfed, Evrysdi should be administered after breastfeeding. Evrysdi should not be mixed with milk or formula milk.

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

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 < 2 months of age have not yet been established (see section *3.1.2 Clinical/Efficacy Studies*).

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. The pregnancy status of female patients of reproductive potential should be verified prior to initiating Evrysdi therapy (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. Prior to initiating treatment, fertility preservation strategies should be discussed with male patients of reproductive potential (see sections *2.5 Use in Special Populations* and *3.3.3 Impairment of Fertility*). The effects of Evrysdi on male fertility have not been investigated in humans.

Retinal Toxicity
The effects of Evrysdi on retinal structure observed in the nonclinical safety studies have not been observed in clinical studies with SMA patients. However, long-term data are still limited. The clinical relevance of these nonclinical findings in the long-term has therefore not been established (see section *3.3.5 Others, Effect on Retinal Structure*).

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

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

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 is not recommended during pregnancy and in women of childbearing potential not using contraception.

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

The safety and efficacy of risdiplam in pediatric patients less than 2 months of age have not yet been established (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 three clinical trials FIREFISH, SUNFISH 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 Part 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 of patients 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-controlled patients and where a causal association with Evrysdi is possible.

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	Diarrhoea	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

The most frequent adverse reactions reported in infantile-onset SMA patients treated with Evrysdi in FIREFISH study were similar to those observed in later-onset SMA patients in SUNFISH study. Additionally, the following adverse reactions were reported in ≥ 10% of patients: upper respiratory tract infection (including nasopharyngitis, rhinitis, respiratory tract infection), pneumonia, constipation, and vomiting.

Table 3 Adverse Drug Reactions Reported in ≥ 5% of Later-Onset SMA Patients Treated with Evrysdi and with An Incidence ≥ 5% Greater Than on Placebo in SUNFISH Part 2 Study

Adverse reaction	Evrysdi n=120 %	Placebo n=60 %
Fever[1]	22	17
Diarrhoea	17	8
Rash[2]	17	2
Mouth and aphthous ulcers	7	0
Arthralgia	5	0
Urinary tract infection[3]	5	0

[1] Includes pyrexia and hyperpyrexia
[2] Includes rash, erythema, rash maculo-papular, rash erythematous, rash popular, dermatitis allergic, and folliculitis
[3] Includes urinary tract infection and cystitis

The adverse reactions diarrhoea 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 Nonclinical Safety*).

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) and SUNFISH (Part 1 and Part 2) studies (see section *3.1.2 Clinical/Efficacy Studies).*

2.6.2 Postmarketing Experience

The following adverse drug reaction has been identified from postmarketing experience with Evrysdi (Table 4). Adverse drug reaction is listed according to system organ classes in MedDRA.

Table 4 Adverse Drug Reaction(s) from Postmarketing Experience

System organ class	Adverse reaction	Frequency category
Skin and subcutaneous tissue disorders	Cutaneous vasculitis[1]	Unknown

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

Cutaneous vasculitis was identified during postmarketing experience. Symptoms recovered after permanent discontinuation of 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 CYP 1A1, 2J2, 3A4 and 3A7. Risdiplam is not a substrate of human multidrug resistance protein 1 (MDR1).

Effects of other medicinal products on Evrysdi
Coadministration 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 coadministered with a CYP3A inhibitor.

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

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 (AUC 11%; C_{max} 16%). The extent of the interaction is not considered clinically relevant, and therefore no dose adjustment is required for CYP3A substrates. 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 coadministration with MATE1/2-K substrates is unknown.

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*).

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 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 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. 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.

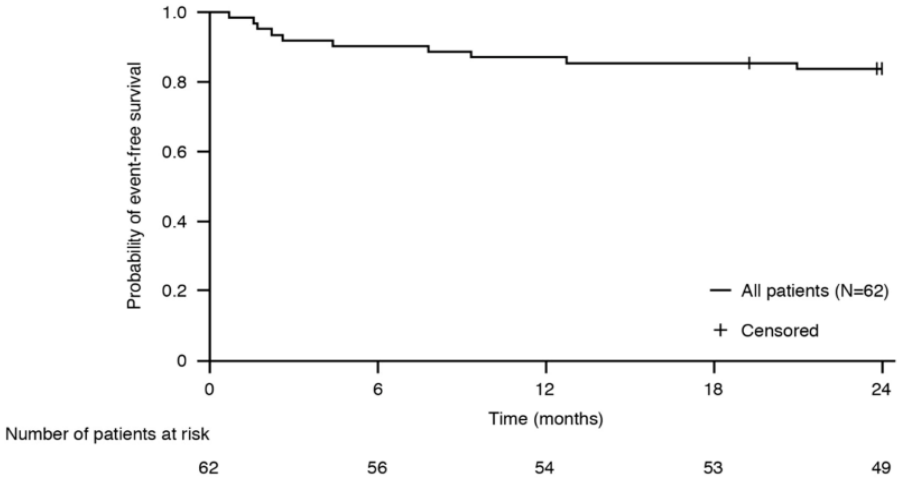
[e] An event is meeting the endpoint of permanent ventilation defined as tracheostomy or ≥ 16 hours of non-invasive ventilation per day or intubation for > 21 consecutive days in the absence of, or following the resolution of, an acute reversible event. Four patients met the endpoint of permanent ventilation 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 enrollment) and one additional patient withdrew from treatment and died 3.5 months later. Four patients required permanent ventilation by Month 24.

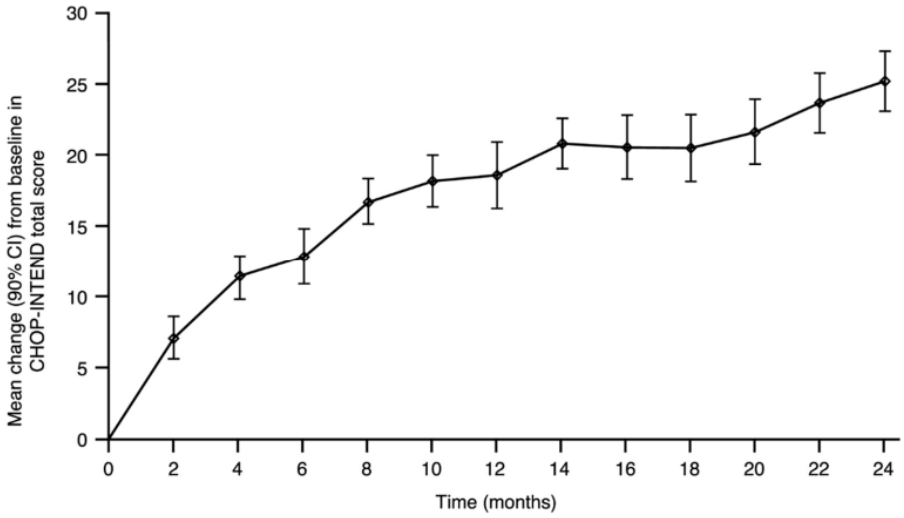
These results indicate a clinically meaningful deviation from the natural history of untreated infantile-onset SMA. Untreated patients with infantile-onset SMA would never be able to sit without support and only 25% would be expected to survive without permanent ventilation beyond 14 months of age.

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

LS: Least Squares

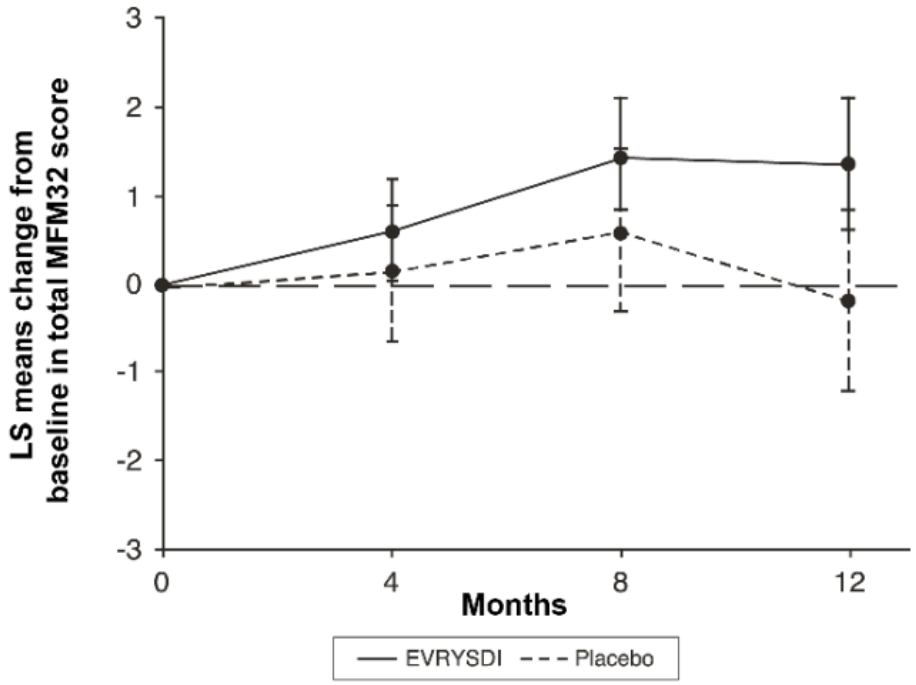
1. Based on the missing data rule for MFM32, 6 patients were excluded from the analysis (Evrysdi n=115; placebo control n=59).
2. Data analysed using a mixed model repeated measure with baseline total score, treatment, visit, age group, treatment-by-visit and baseline-by-visit.
3. Data analysed using 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.

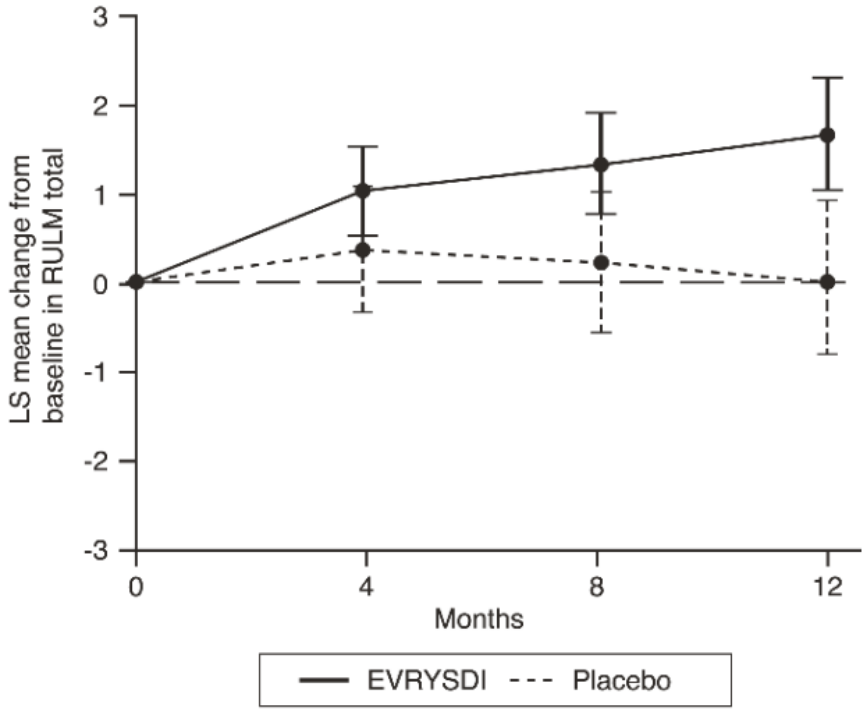
The study also met a secondary independent motor function outcome, RULM. On the RULM, statistically significant and clinically meaningful improvements in motor function were observed after 12 months of treatment compared to baseline. The patients 2-5 years old treated with Evrysdi demonstrated the greatest 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).

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 to 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 were 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% patients had severe scoliosis) and 63% of patients had a Hammersmith Functional Motor Scale Expanded (HFMSE) score < 10 points. The study also included 16 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 aged 1 year to 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 naive 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 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. 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.

3.2.1 Absorption
Risdiplam was rapidly absorbed in the fasted state with a plasma t_{max} ranging from 1 to 4 hours after oral administration. Food (high-fat, high-calorie breakfast) had no relevant effect on the exposure of risdiplam.

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.

Coadministration 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 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 2 months of age.

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

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, embryo-fetal 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.

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.

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

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.

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.

4.2 Special Instructions for Use, Handling and Disposal

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

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

Caution should be exercised in the handling of Evrysdi powder for oral solution (see section *2.4 Warnings and Precautions*). Avoid inhalation and direct contact between 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 7 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.

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

Instructions for administration

Dosing of Evrysdi 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.

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.

Packs
Box of 1 bottle of 2 g powder for oral solution + 1 press-in bottle adapter + 2 reusable oral syringes 1 mL + 2 reusable oral syringes 6 mL + 1 reusable oral syringes 12 mL

Reg. No.: DKI2157511138A1

Medicine: keep out of reach and sight of children
Obat: Jauhkan dari jangkauan dan pandangan anak-anak
On medical prescription only
Harus dengan resep dokter

Made by:
F. Hoffmann-La Roche Ltd., Basel, Switzerland

Released by:
F. Hoffmann-La Roche Ltd., Kaiseraugst, Switzerland

Imported by:
PT Menarini Indria Laboratories, Bekasi, Indonesia

Distributed by:
PT Roche Indonesia, Jakarta, Indonesia

INTRUCTIONS FOR CONSTITUTION (0.75 mg/mL)
EVRYSDI®
(risdiplam) for oral solution

Each EVRYSDI carton contains (see *Figure A*):

1. 1 Cap
2. 1 EVRYSDI bottle
3. 1 Oral syringes 12 mL (in 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 Prescribing Information including Instructions for Constitution (not shown)
8. 1 Patient Information Leaflet including Instructions for Use (not shown)

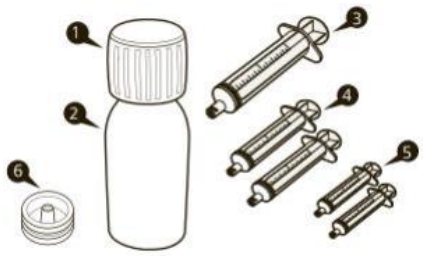


Figure A

Important information about EVRYSDI
- Avoid inhaling EVRYSDI powder.
- **Use gloves.**
- **Do not** use if the powder expiration 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 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
- Do not store the powder (unconstituted medicine) above 25°C (at room temperature) and keep it in the carton.
- Store the solution (constituted medicine) in a refrigerator between 2°C to 8°C.
- Keep the oral solution in the original bottle and always keep the bottle in an upright position with the cap tightly closed.

Constitution

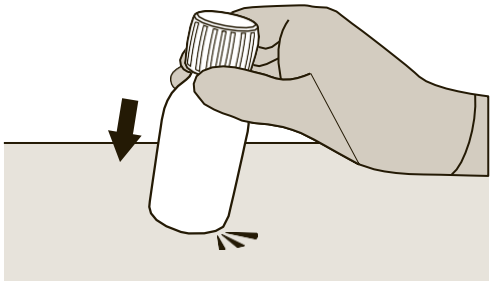


Figure B

Step 1

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

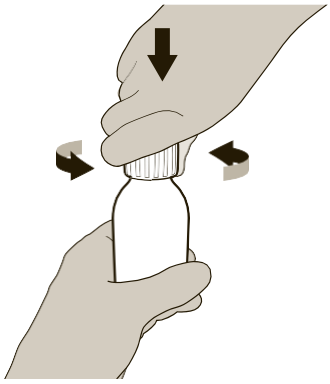


Figure C

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.

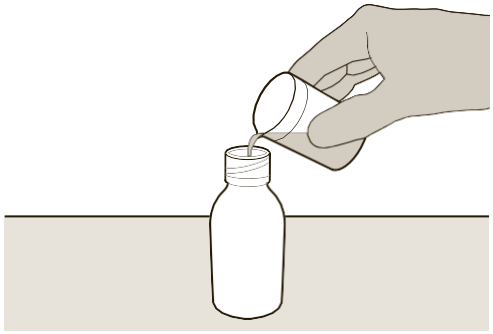


Figure D

Step 3

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

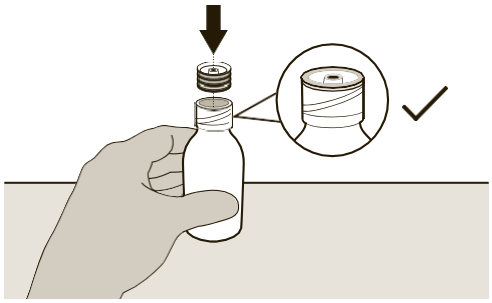


Figure E

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*).

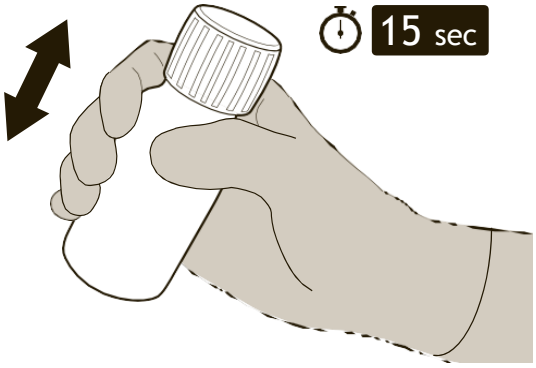


Figure F

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.

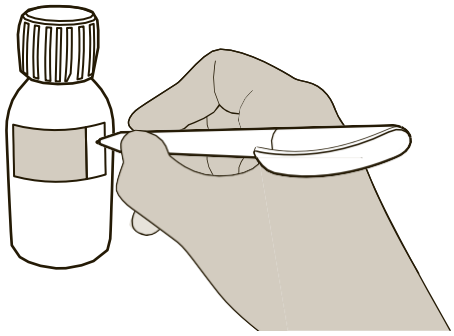


Figure G

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 and the Lot number on the bottle label (see *Figure G*) and carton.

Put the bottle back in its original carton, with syringes (in pouches), Prescribing Information and Patient Information Leaflet. Store the carton in the refrigerator.

(This PI draft has been reviewed and approved for submission by Renata and Asri Mega Putri on 14-Jun-2023)