EVRYSDI®
Risdiplam
0.75 mg/mL Powder for oral solution

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 dihydrate.

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 light yellow, yellow, greyish yellow, greenish yellow, or light green powder.

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.

Treatment with Evrysdi should be initiated and monitored by a specialist medical practitioner experienced in the diagnosis and management of SMA. 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[a] and Body Weight	Recommended Daily Dose
16 days to < 2 months of age	0.15 mg/kg
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

[a] based on corrected age for preterm infants

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 16 days 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 < 16 days of age have not yet been established (see section *3.1.2 Clinical/Efficacy Studies*). 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. 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 16 days 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 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 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*).

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 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 Reaction(s) from Postmarketing Experience

System organ class	Adverse reaction	Frequency category
Skin and subcutaneous tissue 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan
Address: Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Phone: +62-21-4244691 Ext.1079
Website: https://e-meso.pom.go.id/ADR

PT Roche Indonesia
Patient Safety
Email: indonesia.safety@roche.com
Phone: +62 21 3041 3000
Website: https://medinfo.roche.com/id/id.html

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 (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 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*).

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 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.

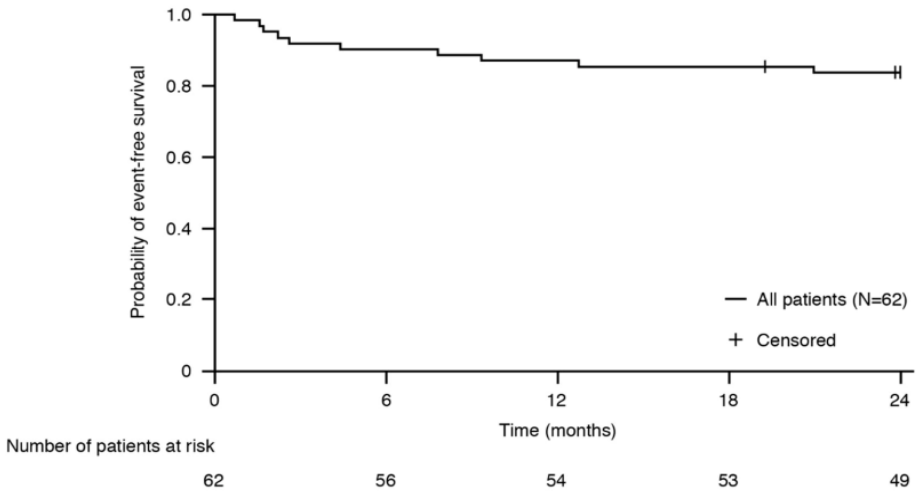
[e] An event is meeting the endpoint of permanent ventilation defined as tracheostomy or ≥ 16 hours of non-invasive ventilation per day or intubation for > 21 consecutive days in the absence of, or following the resolution of, an acute reversible event. Four patients met the endpoint of permanent ventilation 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.

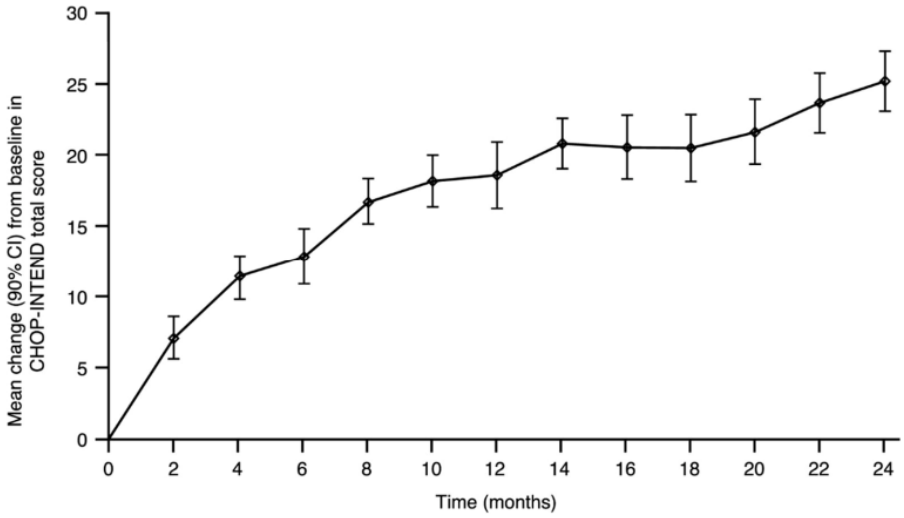
These results indicate a clinically meaningful deviation from the natural history of untreated infantile-onset SMA. Untreated patients with infantile-onset SMA would never be able to sit without support and only 25% would be expected to survive without permanent ventilation beyond 14 months of age.

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)	

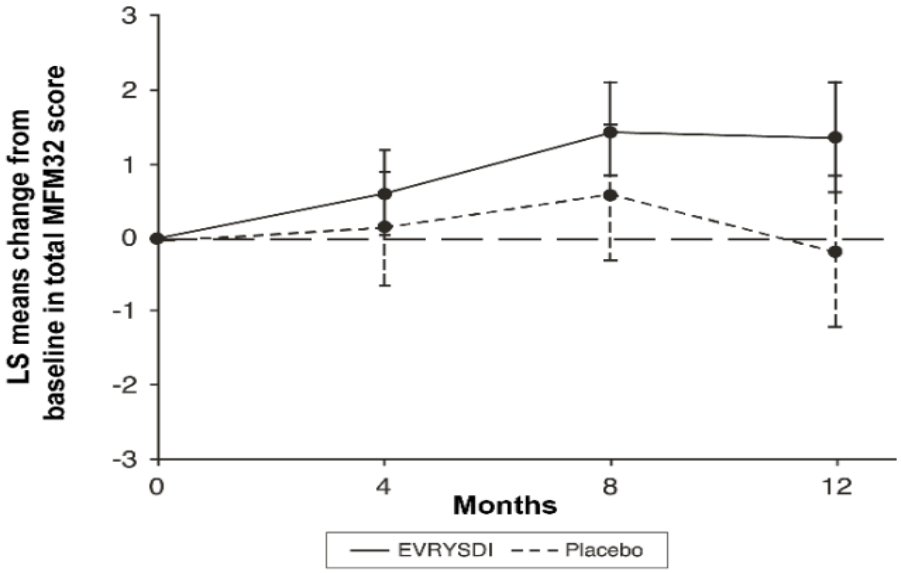
LS: Least Squares

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.

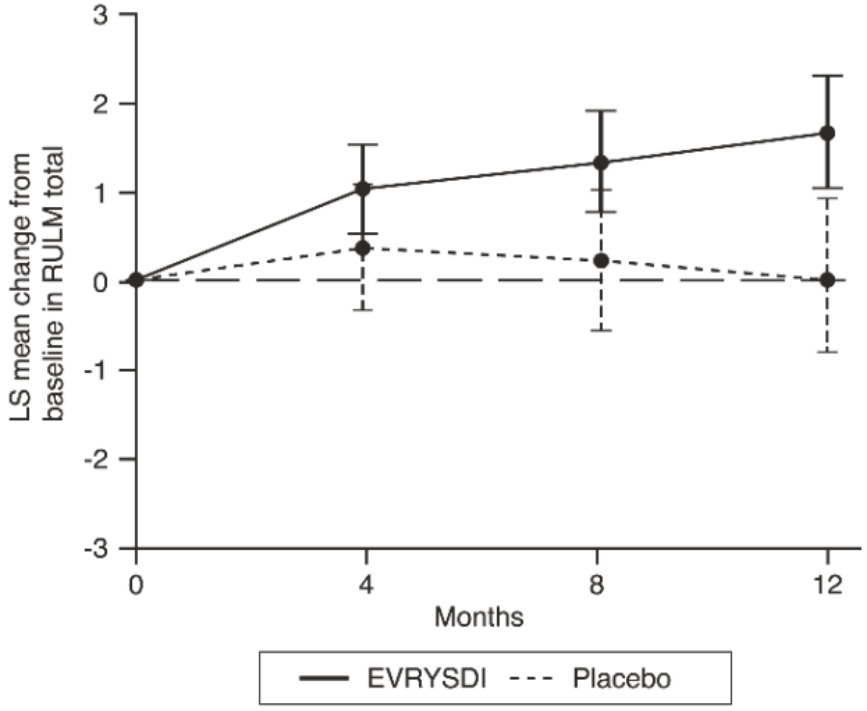
The study also met a secondary independent motor function outcome, RULM. On the RULM, statistically significant and clinically meaningful improvements in motor function were observed after 12 months of treatment compared to baseline. The patients 2-5 years old treated with Evrysdi demonstrated the greatest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

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 and 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 ≥ 1.5 mV. 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 2.6 mV (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 seconds (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

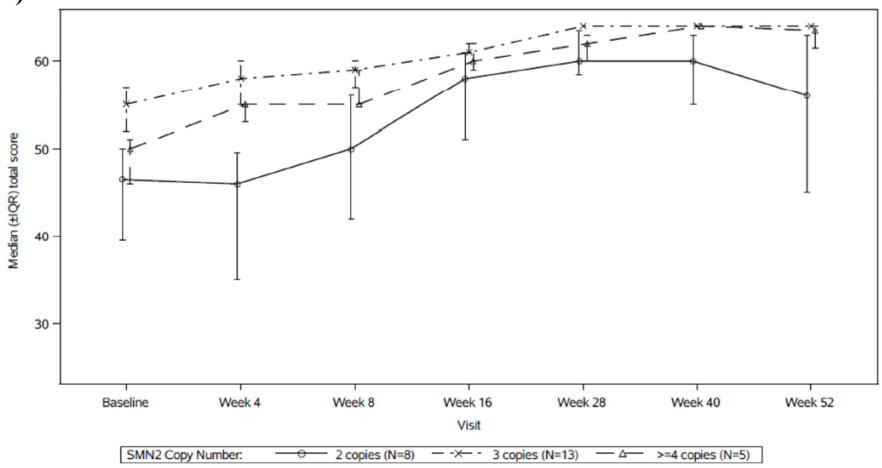
[a] Based on n=25

[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 Motor Neuron 2

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 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 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. 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 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 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.

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.

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 5 mg. 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.

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 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.

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 *2.2 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 syringe 12 mL

Reg. No.: DKI2157511138A1

5. DATE OF LATEST MARKETING AUTHORISATION

Date of latest marketing authorisation: 02 October 2024

6. DATE OF REVISION OF THE PRODUCT INFORMATION

Date of revision of the Product Information:

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 and 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)

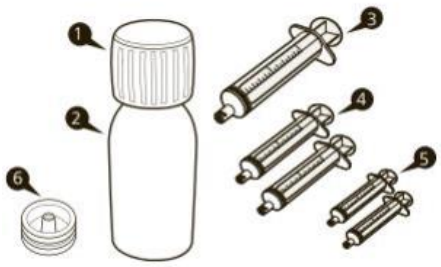


Figure A

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℃ (at room temperature) and keep it in the carton.
- Store the solution (constituted medicine) in a refrigerator between 2℃ to 8℃.
- Keep the oral solution in the original bottle and always keep the bottle in an upright position with the cap tightly closed.

Constitution

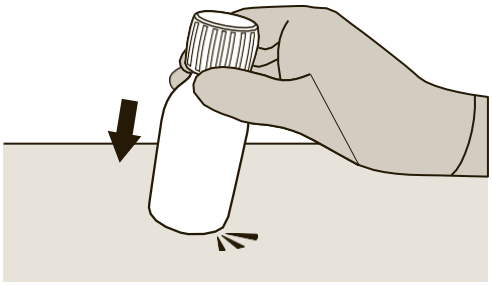


Figure B

Step 1

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

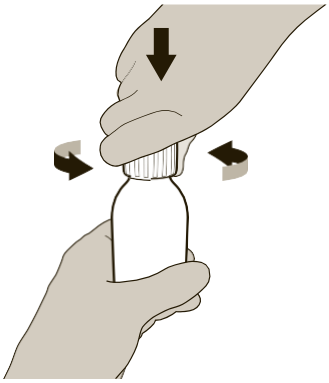


Figure C

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*).

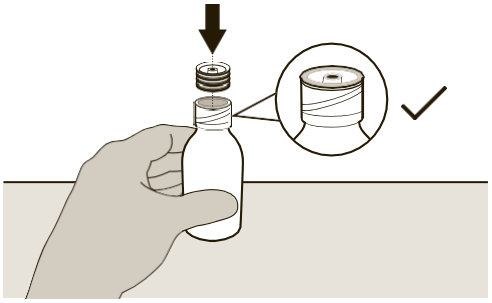


Figure E

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*).

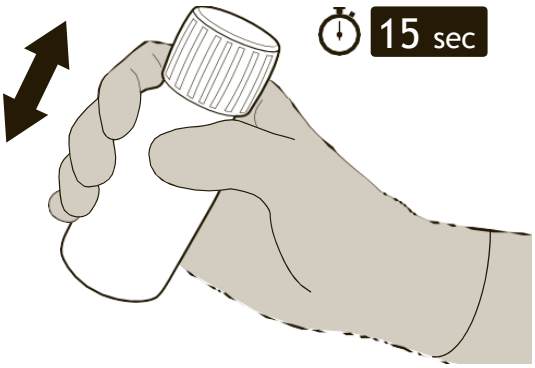


Figure F

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.

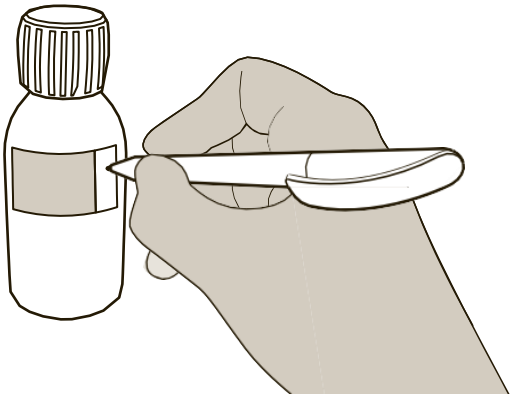


Figure G

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 Asri and Ruth on 28-Nov-2025

INFORMASI PRODUK UNTUK PASIEN

EVRYSDI
Risdiplam
0.75 mg/mL serbuk untuk larutan oral

Bacalah seluruh brosur ini dengan saksama sebelum Anda mulai menggunakan obat ini karena brosur ini berisi informasi yang penting bagi Anda.

- Simpan brosur ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan pada dokter, apoteker atau perawat Anda.
- Obat ini diresepkan hanya untuk Anda. Jangan memberikannya kepada orang lain. Obat ini dapat membahayakan mereka, walaupun tanda-tanda penyakit mereka serupa dengan penyakit Anda.
- Jika Anda mengalami efek samping, bicarakanlah dengan dokter, apoteker atau perawat Anda. Hal ini termasuk efek samping yang mungkin terjadi di luar dari apa yang tercantum pada brosur ini. Lihat bagian 4.

Apa yang terdapat di dalam brosur ini

1. Apa itu EVRYSDI dan kegunaannya

EVRYSDI mengandung zat aktif yaitu "*Risdiplam"*, yang merupakan pengubah penyambung gen *survival motor neuron* 2 (SMN2) yang selektif.

Apa kegunaan dari EVRYSDI
EVRYSDI adalah obat yang digunakan untuk mengobati atrofi otot tulang belakang atau *Spinal Muscular Atrophy* (SMA).

SMA adalah suatu kondisi genetik yang dapat merupakan bawaan lahir, yang disebabkan oleh kekurangan protein yang disebut dengan "*survival of motor neuron*" (SMN) di dalam tubuh. Protein SMN dibutuhkan oleh saraf untuk dapat berfungsi dengan baik. Tidak cukupnya protein SMN berakibat pada hilangnya saraf motorik, yang berujung pada kelemahan otot dan penyusutan otot. Aktivitas dasar seperti kontrol kepala dan leher, duduk, merangkak, dan berjalan dapat terpengaruh. Otot-otot yang digunakan untuk bernapas dan menelan juga dapat terpengaruh.

Bagaimana EVRYSDI bekerja
EVRYSDI bekerja dengan membantu tubuh membentuk lebih banyak protein SMN dan menjaga kadar protein SMN di seluruh tubuh dengan penggunaan yang terus-menerus. Hal ini mengurangi hilangnya sel-sel saraf dan dapat meningkatkan kekuatan serta fungsi otot pada berbagai rentang usia dan tipe SMA.

Pada bayi dengan SMA, EVRYSDI meningkatkan ketahanan hidup, menjaga kemampuan menelan, meningkatkan kesempatan pencapaian dari perkembangan motorik, dan mengurangi kebutuhan rawat inap serta pernafasan menggunakan alat bantu nafas (*ventilator*). Pada anak (bayi berusia 16 hari hingga remaja) dan dewasa, EVRYSDI dapat menjaga serta meningkatkan fungsi motorik seiring waktu.

2. Apa yang perlu Anda ketahui sebelum mengonsumsi EVRYSDI

Jangan konsumsi EVRYSDI jika Anda:

- Alergi terhadap risdiplam atau bahan-bahan lain yang terkandung dalam EVRYSDI. Lihat bagian 6 untuk daftar lengkap isi bahan di dalam EVRYSDI.

Peringatan dan perhatian

Sebelum mengonsumsi EVRYSDI, sampaikan pada dokter, apoteker atau perawat Anda tentang semua kondisi medis Anda.

Jika Anda adalah perempuan sampaikan pada dokter, apoteker atau perawat Anda jika Anda:

- sedang hamil atau berencana untuk hamil
- sedang menyusui atau berencana untuk menyusui

Pengobatan dengan EVRYSDI dapat membahayakan janin Anda atau dapat memengaruhi kesuburan pria. Silakan merujuk pada bagian "**Kehamilan, kontrasepsi, menyusui dan kesuburan**" untuk informasi lebih detail.

Jika Anda pria, sampaikan pada dokter, apoteker atau perawat Anda jika Anda berencana untuk mendonasikan sperma atau memiliki anak.

Kehamilan

- EVRYSDI dapat membahayakan janin Anda. Jika Anda sedang hamil, mengira Anda mungkin hamil, atau berencana untuk hamil, mintalah saran dari dokter Anda sebelum mengonsumsi obat ini. Dokter Anda akan mempertimbangkan manfaat mengonsumsi EVRYSDI bagi Anda dibandingkan risiko terhadap bayi Anda.
- Sebelum Anda memulai pengobatan dengan EVRYSDI, dokter, apoteker atau perawat Anda mungkin akan melakukan tes kehamilan.
- Jika Anda ternyata hamil selama pengobatan dengan EVRYSDI, sampaikan kepada dokter Anda segera. Anda dan dokter Anda akan memutuskan apa yang terbaik untuk Anda dan janin Anda.

Kontrasepsi

Untuk perempuan

Kehamilan sangat tidak dianjurkan:

- selama pengobatan Anda dengan EVRYSDI dan
- selama satu bulan setelah Anda berhenti mengonsumsi EVRYSDI.

Diskusikan dengan dokter Anda tentang metode kontrasepsi yang harus digunakan selama pengobatan dan satu bulan setelah Anda menghentikan pengobatan.

Untuk pria

Jika pasangan perempuan Anda berpotensi hamil, Anda harus mencegah kehamilan. Gunakan metode kontrasepsi yang andal (misalnya kondom):

- selama pengobatan Anda dengan EVRYSDI dan

- selama 4 bulan setelah Anda berhenti mengonsumsi EVRYSDI.

Diskusikan dengan dokter Anda mengenai metode kontrasepsi yang sesuai untuk Anda.

Menyusui
Anda tidak disarankan menyusui selama mengonsumsi obat ini. Hal ini disebabkan belum diketahuinya kemungkinan EVRYSDI masuk ke dalam ASI pada manusia sehingga dapat membahayakan bayi Anda.

Diskusikan dengan dokter, apoteker atau perawat Anda apakah Anda harus berhenti menyusui atau harus berhenti mengonsumsi EVRYSDI.

Kesuburan pria
EVRYSDI dapat berdampak pada kesuburan pria.

Jangan mendonasikan sperma selama pengobatan Anda dan selama 4 bulan setelah Anda berhenti mengonsumsi EVRYSDI.

Jika Anda mempunyai rencana untuk berkeluarga, mintalah saran kepada dokter, apoteker atau perawat Anda.

Obat-obatan lain dan EVRYSDI
Beri tahu dokter, apoteker atau perawat Anda tentang semua obat-obatan yang Anda konsumsi, termasuk obat-obatan dengan resep, obat yang dijual bebas, vitamin, atau suplemen herbal. Simpan daftar obat yang Anda konsumsi untuk ditunjukkan pada dokter, apoteker atau perawat Anda ketika Anda mendapatkan obat baru.

Secara khusus, beri tahukan kepada dokter, apoteker atau perawat apabila Anda sedang atau pernah mengonsumsi obat:
- metformin (obat untuk diabetes melitus tipe 2)
- obat untuk pengobatan SMA

Mengemudi dan menggunakan mesin
EVRYSDI kecil kemungkinannya untuk memengaruhi kemampuan Anda untuk mengemudi dan menggunakan alat atau mesin.

3. Bagaimana cara mengonsumsi EVRYSDI

Bagaimana seharusnya Anda mengonsumsi EVRYSDI
Selalu konsumsi obat ini sesuai dengan anjuran dokter, apoteker atau perawat Anda. Tanyakan kembali dengan dokter, apoteker atau perawat Anda jika Anda tidak yakin.

Anda juga harus membaca dan mengikuti dengan saksama **"Petunjuk penggunaan"** yang terlampir dalam kemasan tentang bagaimana cara mengonsumsi atau memberikan EVRYSDI.

Gunakan spuit oral yang tersedia
Penting bagi Anda untuk menggunakan spuit oral yang disediakan dalam kemasan untuk mengukur dosis EVRYSDI Anda atau anak Anda karena alat tersebut dirancang khusus untuk melindungi obat dari cahaya.

Hubungi dokter, apoteker atau perawat Anda jika spuit oral Anda hilang atau rusak. Mereka akan memberikan saran kepada Anda bagaimana cara untuk tetap dapat mengonsumsi obat Anda.

Seberapa banyak EVRYSDI yang harus dikonsumsi
- **Remaja dan dewasa:** Dosis harian EVRYSDI adalah 5 mg (6,6 mL dari 0,75 mg/mL larutan oral).
- **Bayi dan anak:** Dokter Anda akan menentukan dosis harian EVRYSDI berdasarkan usia dan berat badan anak Anda.

Anda harus mengonsumsi dosis harian sesuai instruksi dokter Anda. Jangan mengubah dosis tanpa menyampaikannya terlebih dahulu kepada dokter Anda.

Jika Anda tidak dapat menelan keseluruhan dosis, atau mengalami muntah setelah mengonsumsi dosis EVRYSDI yang dianjurkan, jangan mengonsumsi dosis tambahan. Konsumsi dosis selanjutnya pada waktu yang sama di hari berikutnya.

Kapan dan bagaimana cara mengonsumsi EVRYSDI
- EVRYSDI adalah cairan, dan disebut sebagai ‘larutan’ atau ‘obat’ pada brosur ini.
- Konsumsi EVRYSDI satu hari sekali setelah makan pada waktu yang sama setiap harinya. Hal ini akan membantu Anda mengingat kapan harus mengonsumsi obat Anda.
- Minum air setelah mengonsumsi obat. Jangan mencampur obat dengan susu atau susu formula.
- Ambil dan berikan EVRYSDI segera setelah diambil menggunakan spuit. Apabila obat tidak diminum dalam 5 menit, buang obat dari dalam spuit dan ambil kembali dosis yang baru.
- Apabila EVRYSDI mengenai kulit anak Anda, bersihkan area yang terkena obat dengan air dan sabun.

Seberapa lama mengonsumsi EVRYSDI
Dokter, apoteker atau perawat Anda akan memberi tahu Anda berapa lama Anda perlu mengonsumsi EVRYSDI. Jangan menghentikan pengobatan EVRYSDI kecuali dokter, apoteker atau perawat Anda menyarankan demikian.

Jika Anda mengonsumsi EVRYSDI lebih dari seharusnya
Jika Anda mengonsumsi EVRYSDI lebih dari seharusnya, sampaikan ke dokter atau pergi ke rumah sakit segera. Bawa kemasan obat dan brosur ini bersama Anda.

Jika Anda lupa mengonsumsi EVRYSDI
- Jika terjadi dalam 6 jam dari waktu Anda biasa mengonsumsi EVRYSDI, konsumsi dosis yang tertinggal segera setelah Anda ingat.
- Jika sudah lewat 6 jam dari waktu Anda biasa mengonsumsi EVRYSDI, lewati dosis yang tertinggal tersebut dan konsumsi dosis selanjutnya pada waktu waktu yang sama di hari berikutnya.

Jangan konsumsi dosis ganda untuk mengganti dosis yang terlupakan.

4. Kemungkinan efek samping

Seperti semua obat, EVRYSDI dapat menyebabkan efek samping, walaupun tidak semua pasien mengalaminya.

Efek samping yang paling umum dari EVRYSDI meliputi (dapat terjadi pada lebih dari 1 dari 10 orang):

Untuk *later-onset SMA*

- demam
- diare
- ruam

Untuk *infantile-onset SMA*

- demam
- diare
- ruam
- hidung berair, bersin, radang tenggorokan dan batuk (infeksi saluran napas atas)
- infeksi paru-paru
- konstipasi (susah buang air besar)
- muntah

Efek samping yang jarang muncul (dapat terjadi hingga pada 1 dari 100 orang):

- detak jantung yang cepat (takikardia)

Efek samping yang tidak diketahui (frekuensi tidak dapat diperkirakan dari data yang tersedia):

- peradangan pada pembuluh darah kecil terutama yang mengenai bagian kulit (*cutaneous vasculitis)*

Jika Anda mengalami salah satu dari efek samping tersebut, sampaikan ke dokter, apoteker, atau perawat Anda. Hal ini juga termasuk efek samping lainnya yang tidak tercantum pada brosur ini.

Pelaporan efek samping

Bila Anda mengalami efek samping, beri tahu dokter, apoteker atau perawat Anda. Termasuk efek samping apa pun yang mungkin terjadi tetapi tidak tertera pada brosur ini. Anda juga dapat melaporkan efek samping langsung melalui:

PT Roche Indonesia – Patient Safety
Email: Indonesia.safety@roche.com
Tel: +62 21 3041 3000
Situs web: https://medinfo.roche.com/id/id.html

Dengan melaporkan efek samping, Anda dapat membantu memberikan lebih banyak informasi mengenai keamanan obat ini.

5. Bagaimana cara penyimpanan EVRYSDI

- Jauhkan obat ini dari pandangan dan jangkauan anak-anak.
- Simpan larutan oral di lemari pendingin pada suhu 2°C hingga 8°C. Jangan dibekukan.
- Apabila perlu, Anda atau pengasuh Anda dapat menyimpan larutan oral pada suhu ruang (di bawah 40°C) selama tidak lebih dari 5 hari.
- Simpan larutan oral dalam botol kaca yang didapat dalam kemasan.
- Simpan botol larutan oral dalam posisi tegak.
- Ketika larutan oral dipindahkan dari botol ke spuit oral, segera konsumsi EVRYSDI. Jangan simpan larutan EVRYSDI di dalam spuit oral.

- Cuci spuit oral sesuai dengan instruksi setelah penggunaan. Jangan buang spuit oral tersebut.
- Larutan oral dapat dikonsumsi selama 64 hari setelah dilarutkan oleh petugas kesehatan Anda saat disimpan di lemari pendingin pada suhu 2°C hingga 8°C. Buang obat setelah melewati tanggal "DISCARD AFTER (tanggal batas konsumsi)" yang tertulis di label botol atau buang obat apabila botol telah disimpan pada suhu ruang (di bawah 40°C) selama lebih dari 5 hari. Buang obat apabila botol telah disimpan pada suhu di atas 40°C.

6. Isi kemasan dan informasi lainnya

Anda akan menerima EVRYSDI dari dokter, apoteker atau perawat Anda dalam bentuk larutan untuk pemberian secara oral yang dapat diberikan melalui mulut atau selang makanan. Larutan tersebut disiapkan oleh dokter, apoteker atau perawat Anda. Jika obat dalam botol masih dalam bentuk serbuk, jangan dikonsumsi. Hubungi dokter, apoteker atau perawat Anda untuk menyiapkan menjadi larutan.

Apa isi EVRYSDI dan seperti apa bentuk EVRYSDI

- Zat aktifnya adalah risdiplam.
- Komposisi lainnya (zat tambahan) adalah mannitol, isomalt, perasa stroberi, asam tartarat, natrium benzoat, polietilen glikol, sucralose, asam askorbat, dan dinatrium edetat dihidrat.
- Tiap botol 100 mL EVRYSDI berisi 2,0 g serbuk yang mengandung 60 mg risdiplam. Serbuk berwarna kuning muda, kuning, kuning keabu-abuan, kuning kehijauan, atau hijau muda.
- Setelah dilarutkan/direkonstitusikan, volume larutan adalah 80 mL. Larutan oral tersebut berwarna kuning kehijauan hingga kuning dengan rasa stroberi. Setiap mL dari larutan tersebut mengandung 0,75 mg risdiplam.
- Tiap kemasan EVRYSDI berisi 1 botol, 1 botol adaptor tekan, 2 spuit oral 1 mL yang dapat digunakan kembali, 2 spuit oral 6 mL yang dapat digunakan kembali dan 1 spuit oral 12 mL yang dapat digunakan kembali.

Kemasan

Dus, 1 botol @ 2 g serbuk + 1 botol adaptor tekan
+ 2 spuit oral 1 mL yang dapat digunakan kembali
+ 2 spuit oral 6 mL yang dapat digunakan kembali
+ 1 spuit oral 12 mL yang dapat digunakan kembali

Nomor registrasi: DKI2157511138A1

Obat: jauhkan dari pandangan dan jangkauan anak-anak

HARUS DENGAN RESEP DOKTER

Diproduksi dan dirilis oleh:
F. Hoffmann-La Roche Ltd., Kaiseraugst, Swiss

Diimpor oleh:
PT Menarini Indria Laboratories, Bekasi, Indonesia

Didistribusikan oleh:
PT Roche Indonesia, Jakarta, Indonesia

7. Petunjuk penggunaan

Petunjuk Penggunaan EVRYSDI
Serbuk untuk larutan oral

Pastikan Anda membaca dan memahami Petunjuk Penggunaan ini sebelum Anda mulai menggunakan EVRYSDI untuk mendapatkan informasi mengenai bagaimana menyiapkan dan memberikan EVRYSDI melalui spuit oral, selang gastrostomi (*G-tube*) atau selang nasogastrik (*NG-tube*).

Jika Anda memiliki pertanyaan bagaimana cara menggunakan EVRYSDI, hubungi dokter, apoteker atau perawat Anda.

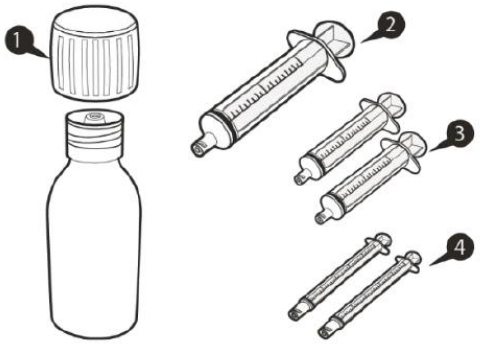
Anda akan menerima EVRYSDI dalam bentuk larutan di dalam botol. Jangan gunakan jika obat di dalam botol berupa serbuk dan segera hubungi dokter, apoteker atau perawat Anda.

Informasi Penting Terkait EVRYSDI

- Tanyakan kepada dokter, apoteker atau perawat Anda mengenai spuit oral yang tepat yang harus Anda gunakan dan bagaimana cara mengukur dosis harian yang telah diresepkan.
- Selalu gunakan spuit oral yang dapat digunakan kembali yang disediakan di kemasan untuk mengukur dosis harian yang telah diresepkan. Spuit oral ini melindungi obat dari cahaya.
- Dua buah spuit oral dengan ukuran masing-masing tersedia untuk mengantisipasi jika salah satu hilang atau rusak. Hubungi dokter, apoteker atau perawat Anda jika kedua spuit oral tersebut hilang atau rusak. Mereka akan memberikan saran bagaimana melanjutkan pengobatan Anda.
- Lihat bagian "**Cara memilih spuit oral yang tepat untuk digunakan pada dosis harian EVRYSDI sesuai resep Anda**", untuk mengetahui spuit oral yang harus Anda gunakan. Tanyakan kepada dokter, apoteker atau perawat Anda jika Anda memiliki pertanyaan untuk memilih spuit oral.
- Jika adaptor botol tidak terdapat pada botol, **jangan** gunakan EVRYSDI dan segera hubungi dokter, apoteker atau perawat Anda.
- Jangan gunakan EVRYSDI setelah tanggal **Discard after** yang tertera pada label botol. Tanyakan kepada dokter, apoteker atau perawat Anda jika tanggal **Discard after** tidak tertera pada label botol.
- **Jangan** campurkan EVRYSDI ke dalam makanan atau cairan (contohnya: susu atau susu formula).
- **Jangan** gunakan EVRYSDI jika botol atau spuit oral rusak.
- **Hindari** paparan EVRYSDI pada kulit Anda. Jika kulit Anda terpapar EVRYSDI, cuci area yang terpapar dengan menggunakan sabun dan air.
- Jika Anda menumpahkan EVRYSDI, keringkan area tersebut dengan handuk dan cuci dengan menggunakan sabun dan air. Buang handuk tersebut dan cuci tangan Anda dengan baik menggunakan sabun dan air.
- Jika EVRYSDI yang tersisa dalam botol tidak mencukupi dosis harian Anda, buang botol beserta isinya dan spuit oral bekas ke tempat pembuangan obat; gunakan botol EVRYSDI yang baru untuk mendapatkan dosis harian Anda. **Jangan mencampurkan** EVRYSDI dari botol baru dengan botol yang saat ini sedang Anda gunakan.

Tiap kemasan EVRYSDI berisi *(Lihat Gambar A)*

1. 1 botol EVRYSDI dengan adaptor dan tutup botol
2. 1 spuit oral 12 mL yang dapat digunakan kembali (dalam plastik)
3. 2 spuit oral 6 mL yang dapat digunakan kembali (dalam plastik)
4. 2 spuit oral 1 mL yang dapat digunakan kembali (dalam plastik)
5. 1 Informasi Produk untuk Pasien termasuk Petunjuk Penggunaan (tidak nampak pada Gambar A



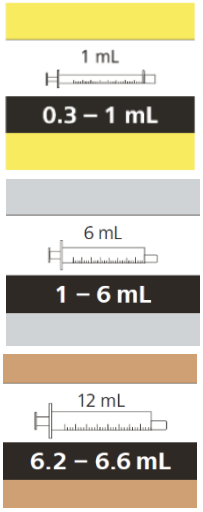
Gambar A

Bagaimana cara penyimpanan EVRYSDI
Silakan merujuk pada bagian *5. Bagaimana cara penyimpanan EVRYSDI* untuk informasi lebih lengkap.

A) Menyiapkan dan mengambil dosis harian Anda

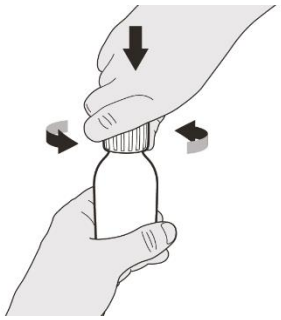
Cara memilih spuit oral yang tepat untuk digunakan pada dosis harian EVRYSDI sesuai resep Anda

- Jika dosis harian EVRYSDI Anda adalah antara 0.3 mL dan 1 mL, gunakan spuit oral 1 mL (label kuning).
- Jika dosis harian EVRYSDI Anda adalah antara 1 mL dan 6 mL, gunakan spuit oral 6 mL (label abu-abu).
- Jika dosis harian EVRYSDI sesuai resep Anda adalah 6,2 mL atau lebih, gunakan spuit oral 12 mL (label cokelat).



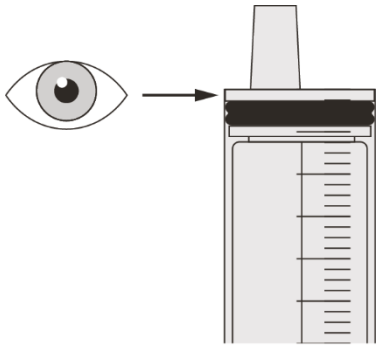
Tanyakan kepada dokter, apoteker atau perawat Anda mengenai pembulatan dosis harian Anda atau anak Anda terhadap penanda spuit terdekat.

Cara untuk menyiapkan dosis harian EVRYSDI Anda



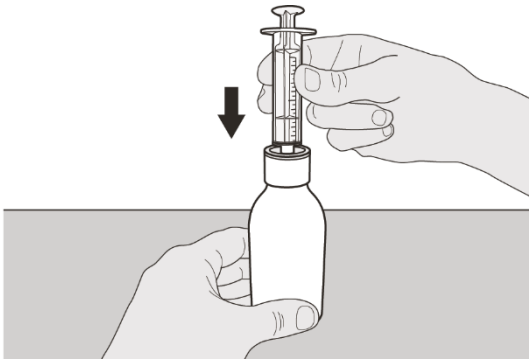
Gambar B

Langkah A1
Buka tutup botol dengan cara mendorongnya ke bawah lalu putar tutup ke kiri (melawan arah jarum jam) (Lihat *Gambar* B). Jangan buang tutup botol.



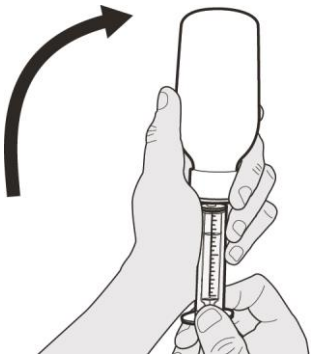
Gambar C

Langkah A2
Tekan piston pada spuit oral seluruhnya untuk membuang semua udara yang terdapat dalam spuit oral. (Lihat *Gambar* C).



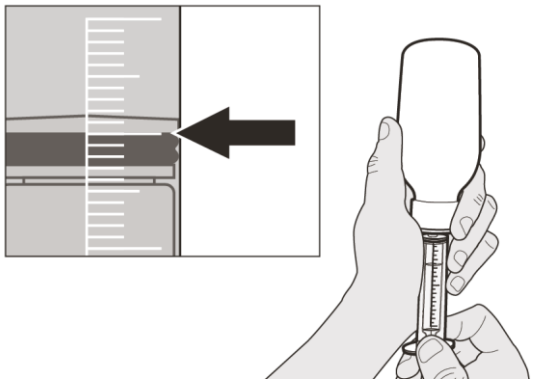
Gambar D

Langkah A3
Jaga botol pada posisi tegak, masukkan ujung spuit oral ke dalam adaptor botol. (Lihat *Gambar* D).



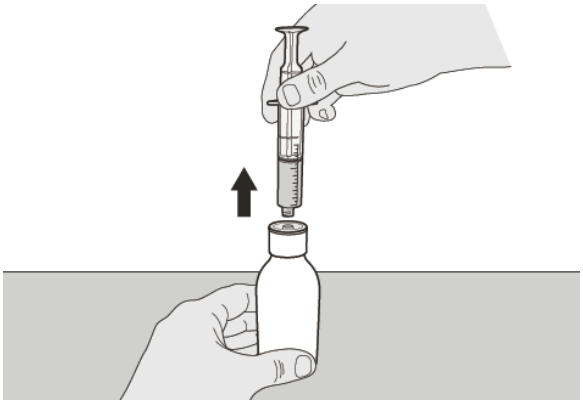
Gambar E

Langkah A4
Balikkan botol secara hati-hati dengan ujung spuit oral masuk dengan rapat ke dalam adaptor botol (Lihat *Gambar* E).



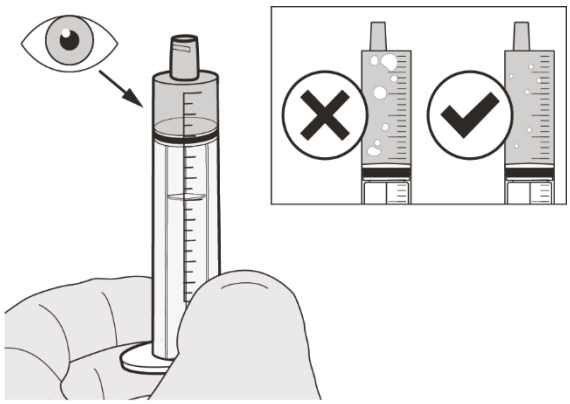
Gambar F

Langkah A5
Tarik kembali piston perlahan-lahan untuk mengambil dosis harian EVRYSDI Anda. Bagian atas dari piston yang berwarna hitam harus sejajar dengan tanda mL pada spuit oral untuk dosis harian sesuai resep Anda (Lihat *Gambar* F).
Setelah dosis yang tepat diambil, **tahan posisi piston supaya tidak bergerak/tidak bergeser**.



Gambar G

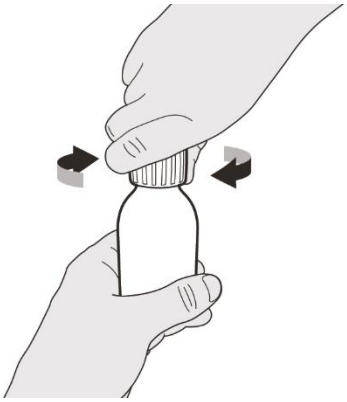
Langkah A6
Terus tahan posisi piston supaya tidak bergerak/tidak bergeser. Biarkan spuit oral tetap terhubung dengan adaptor botol dan kembalikan botol ke posisi tegak. Letakkan botol pada permukaan yang datar. Lepaskan spuit oral dari adaptor botol dengan menarik spuit oral lurus ke atas secara perlahan (Lihat *Gambar* G).



Gambar H

Langkah A7
Tahan spuit oral dengan ujung menghadap ke atas. Periksa larutan obat yang berada dalam spuit oral. **Jika** terdapat banyak gelembung udara besar dalam spuit oral (Lihat *Gambar* H) **atau jika** Anda mengambil dosis harian EVRYSDI yang salah, masukkan kembali dengan rapat ujung spuit oral ke dalam adaptor botol. Tekan piston ke bawah sehingga seluruh larutan obat masuk kembali ke dalam botol dan ulangi Langkah A4 hingga A7.

Konsumsi atau berikan EVRYSDI segera setelah larutan obat diambil ke dalam spuit oral. Jika tidak dikonsumsi **dalam 5 menit**, buang larutan obat dari spuit oral dan siapkan dosis yang baru.



Gambar I

Langkah A8
Pasang kembali tutup pada botol. Putar tutup ke kanan (sesuai arah jarum jam) untuk menutup botol dengan rapat (Lihat *Gambar* I). Jangan melepas adaptor botol dari botolnya.

Jika Anda mengonsumsi dosis harian EVRYSDI Anda melalui mulut, ikuti instruksi pada **"B) Cara mengonsumsi dosis harian EVRYSDI melalui mulut".**

Jika Anda mengonsumsi dosis harian EVRYSDI Anda melalui selang gastrostomi, ikuti instruksi pada **"C) Cara memberikan dosis harian EVRYSDI melalui selang gastrostomi".**

Jika Anda mengonsumsi dosis harian EVRYSDI Anda melalui selang nasogastrik, ikuti instruksi pada **"D) Cara memberikan dosis harian EVRYSDI melalui selang nasogastrik".**

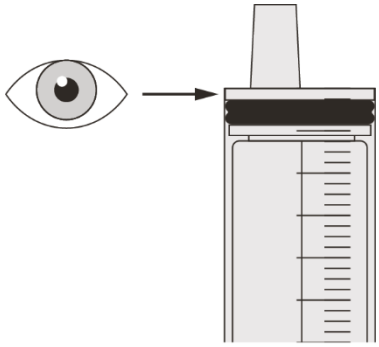
Spuit oral EVRYSDI dirancang khusus agar kompatibel dengan sistem ENFit®. Jika selang makan Anda tidak kompatibel dengan ENFit®, Anda mungkin memerlukan konektor transisi ENFit® untuk menghubungkan spuit oral EVRYSDI ke selang gastrostomi atau nasogastrik Anda.

B) Cara mengonsumsi dosis harian EVRYSDI melalui mulut

Duduk tegak ketika mengonsumsi dosis harian EVRYSDI melalui mulut.

Gambar J

Langkah B1
Masukkan spuit oral ke dalam mulut **dengan ujungnya berada pada salah satu pipi.**
Tekan piston seluruhnya secara **perlahan** untuk memberikan seluruh dosis EVRYSDI (Lihat *Gambar* J).
Memberikan EVRYSDI langsung ke tenggorokan atau terlalu cepat dapat mengakibatkan tersedak.



Gambar K

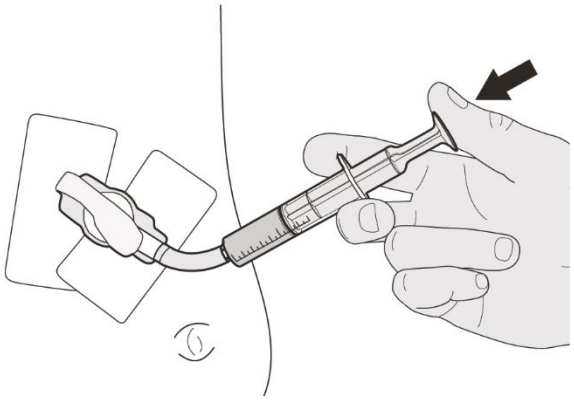
Langkah B2
Pastikan bahwa tidak ada obat yang tersisa di dalam spuit oral (Lihat *Gambar* K).

Gambar L

Langkah B3
Minum air segera setelah mengonsumsi dosis EVRYSDI sesuai resep (Lihat *Gambar* L).
Lanjutkan ke **Langkah E untuk cara membersihkan spuit oral.**

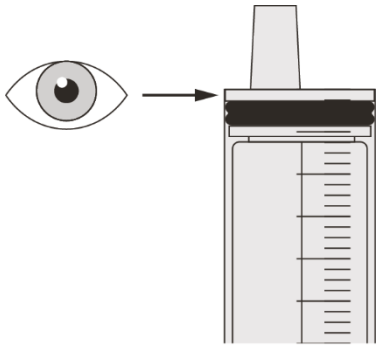
C) Cara memberikan dosis harian EVRYSDI melalui selang gastrostomi

Jika Anda memberikan EVRYSDI melalui selang gastrostomi, minta dokter, apoteker atau perawat Anda untuk menunjukkan kepada Anda cara memeriksa selang gastrostomi sebelum memberikan EVRYSDI.



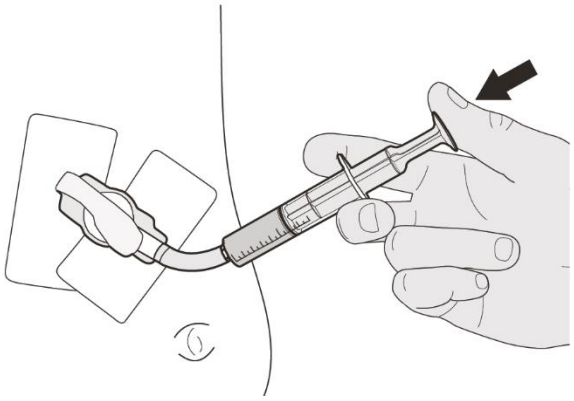
Gambar M

Langkah C1
Masukkan ujung spuit oral ke dalam selang gastrostomi. Tekan piston perlahan-lahan seluruhnya untuk memberikan dosis penuh EVRYSDI (Lihat *Gambar* M).



Gambar N

Langkah C2
Pastikan bahwa tidak ada larutan obat yang tersisa di dalam spuit oral (Lihat *Gambar* N).



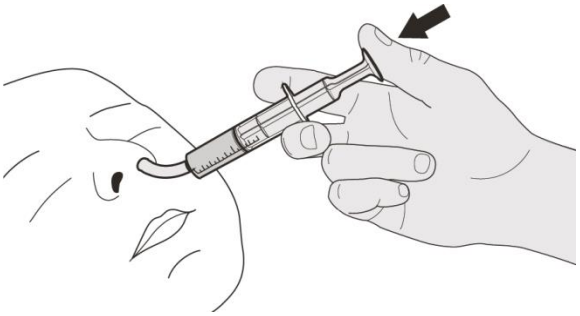
Gambar O

Langkah C3
Bilas segera selang gastrotomi dengan air sebanyak 10 sampai 20 mL setelah memberikan dosis EVRYSDI sesuai resep (Lihat *Gambar* O).

Lanjutkan ke **Langkah E untuk cara membersihkan spuit oral.**

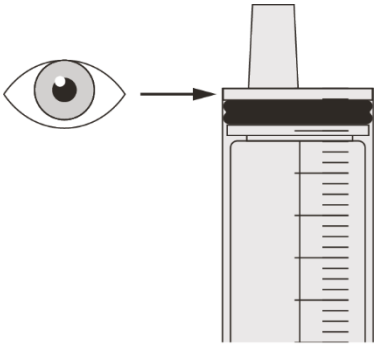
D) Cara memberikan dosis harian EVRYSDI melalui selang nasogastrik

Jika Anda memberikan EVRYSDI melalui selang nasogastrik, minta dokter, apoteker atau perawat Anda untuk menunjukkan kepada Anda cara memeriksa selang nasogastrik sebelum memberikan EVRYSDI.



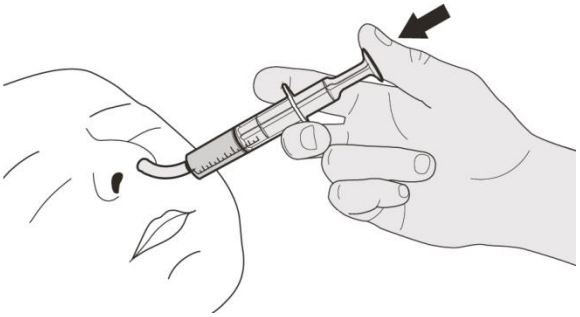
Gambar P

Langkah D1
Masukkan ujung spuit oral ke dalam selang nasogastrik. Tekan piston seluruhnya secara perlahan untuk memberikan seluruh dosis EVRYSDI (Lihat *Gambar* P).



Gambar Q

Langkah D2
Pastikan bahwa tidak ada larutan obat yang tersisa di dalam spuit oral (Lihat *Gambar* Q).

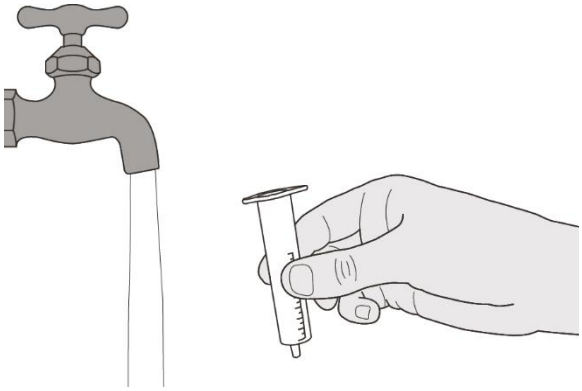


Gambar R

Langkah D3
Bilas segera selang nasogastrik dengan air sebanyak 10 sampai 20 mL setelah memberikan dosis EVRYSDI sesuai resep (Lihat *Gambar* R).

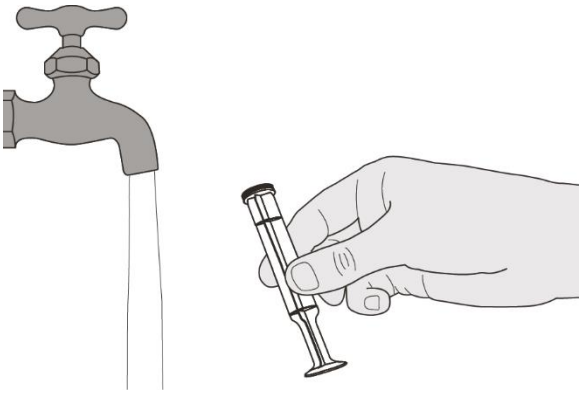
Lanjutkan ke **Langkah E untuk cara membersihkan spuit oral.**

E) Cara membersihkan spuit oral setelah digunakan



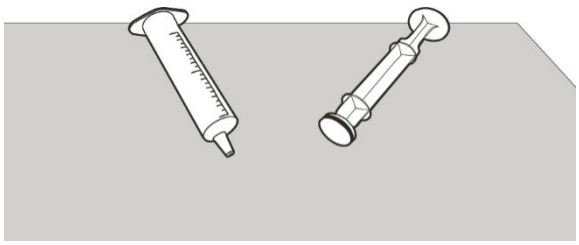
Gambar S

Langkah E1
Lepaskan piston dari spuit oral.
Bilas tabung spuit oral dengan baik di bawah air bersih mengalir (Lihat *Gambar* S).



Gambar T

Langkah E2
Bilas piston dengan baik di bawah air bersih mengalir (Lihat *Gambar* T).



Gambar U

Langkah E3
Pastikan tabung spuit oral dan piston sudah bersih.

Untuk pengeringan, letakkan tabung spuit oral dan piston pada permukaan yang bersih di tempat yang aman (Lihat *Gambar* U).

Cuci tangan Anda. Setelah kering, pasang kembali piston ke dalam tabung spuit oral dan simpan spuit oral bersama botol larutan obat Anda, di dalam kemasannya.