Evrysdi®

Risdiplam

Powder for oral Solution

1. NAME OF THE MEDICINAL PRODUCT

Evrysdi

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bottle contains 60 mg risdiplam in 2 g powder for oral solution.

Each mL of the constituted solution contains 0.75 mg risdiplam.

Excipients with known effects

Each mL contains 0.38 mg of sodium benzoate and 2.97 mg of isomalt.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral solution. Light yellow, yellow, greyish yellow, greenish yellow, or light green powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EVRYSDI is indicated for the treatment of spinal muscular atrophy (SMA) types 1, 2 and 3 in pediatric and adult patients

4.2 Posology and method of administration

Treatment with Evrysdi should be initiated by a physician with experience in the management of SMA.

Posology

The recommended once daily dose of Evrysdi is determined by age and body weight (see Table 1). Evrysdi is taken orally once a day after a meal at approximately the same time each day.

Table 1. Dosing regimen by age and body weight

Age and body weight	***Recommended daily dose***
< 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

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

Delayed or missed doses
If a planned dose is missed, it should be administered as soon as possible if still within 6 hours of the scheduled dose. Otherwise, the missed dose should be skipped and the next dose should be administered at the regularly scheduled time the next day.

If a dose is not fully swallowed or vomiting occurs after taking a dose of Evrysdi, another dose should not be administered to make up for the incomplete dose. The next dose should be administered at the regularly scheduled time.

Elderly
No dose adjustment is required in elderly patients based on limited data in subjects aged 65 years and older (see section 5.2).

Renal impairment
Risdiplam has not been studied in this population. No dose adjustment is expected to be required in patients with renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment is required in patients with mild or moderate hepatic impairment. Patients with severe hepatic impairment have not been studied and may have increased risdiplam exposure (see sections 5.1 and 5.2).

Paediatric population

Use of Evrysdi for SMA in patients 2 months of age and younger is supported by pharmacokinetic and safety data from paediatric patients 16 days and older (see sections 4.8, 5.1 and 5.2), and pharmacokinetic modeling and simulation to identify the dosing regimen. No data on risdiplam pharmacokinetics are available in patients less than 16 days of age

Method of administration

Oral use.

Evrysdi must be constituted by a healthcare professional (e.g. pharmacist) prior to being dispensed. It is recommended that a healthcare professional (HCP) discuss with the patient or caregiver how to prepare the prescribed daily dose prior to administration of the first dose.

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

Evrysdi should be taken immediately after it is drawn up into the oral syringe. If it is not taken within 5 minutes, it should be discarded from the oral syringe and a new dose be prepared. If Evrysdi spills or gets on the skin, the area should be washed with soap and water.

The patient should drink water after taking Evrysdi to ensure the medicinal product has been completely swallowed. If the patient is unable to swallow and has a nasogastric or gastrostomy tube *in situ*, Evrysdi can be administered via the tube. The tube should be flushed with water after delivering Evrysdi.

Selection of the oral syringe for the prescribed daily dose:

Syringe size	*Dosing volume*	*Syringe markings*
1 mL	0.3 mL to 1 mL	0.01 mL
6 mL	1 mL to 6 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. The dose volume should be rounded to the nearest graduation mark on the selected oral syringe.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Potential embryo-foetal toxicity

Embryo-foetal toxicity has been observed in animal studies (see section 5.3). 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 in female patients, and 4 months after the last dose in male patients. The pregnancy status of female patients of reproductive potential should be verified prior to initiating Evrysdi therapy (see section 4.6).

Potential effects 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 4.6 and 5.3). 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 non-clinical 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 5.3).

Excipients

Isomalt
Evrysdi contains isomalt (2.97 mg per mL). Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Sodium
Evrysdi contains 0.375 mg of sodium benzoate per mL. Sodium benzoate may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

Evrysdi contains less than 1 mmol sodium (23 mg) per 5 mg dose, i.e. is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Risdiplam is primarily metabolized by hepatic enzymes flavin monooxygenase 1 and 3 (FMO1 and 3), and also by cytochrome P450 enzymes (CYPs) 1A1, 2J2, 3A4, and 3A7. Risdiplam is not a substrate of human multidrug resistance protein 1 (MDR1).

Effects of other medicinal products on risdiplam

Co-administration of 200 mg itraconazole twice daily, a strong CYP3A inhibitor, with a single oral dose of 6 mg risdiplam did not exhibit a clinically relevant effect on the PK parameters of risdiplam (11% increase in AUC, 9% decrease in C_{max}). No dose adjustments are required when Evrysdi is co-administered with a CYP3A inhibitor.

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

Effects of risdiplam on other medicinal products

Risdiplam is a weak inhibitor of CYP3A. In healthy adult subjects, oral administration of risdiplam 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.

In vitro studies have shown that risdiplam and its major human metabolite M1 are not significant inhibitors of human MDR1, organic anion-transporting polypeptide (OATP)1B1, OATP1B3, organic anion transporter 1 and 3 (OAT 1 and 3). However, risdiplam and its metabolite are *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. The effect of co-administration of risdiplam on the pharmacokinetics of MATE1 and MATE2-K substrates in humans is unknown. Based on *in vitro* data, risdiplam may increase plasma concentrations of medicinal products eliminated via MATE1 or MATE2-K, such as metformin. If co-administration cannot be avoided, drug-related toxicities should be monitored and dosage reduction of the co-administered medicinal product should be considered if needed.

There is no efficacy or safety data to support the concomitant use of risdiplam and nusinersen.

The potential for synergistic effects of concomitant administration of risdiplam with retinotoxic drugs has not been studied. Therefore, caution in using concomitant medications with known or suspected retinal toxicity is recommended.

4.6 Fertility, pregnancy and lactation

Patients of reproductive potential

Contraception in male and female patients
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 and for at least 1 month after the last dose.

- Male patients, and their female partners of childbearing potential, should both ensure that highly effective contraception is achieved during treatment and for at least 4 months after the last dose.

Pregnancy testing

The pregnancy status of female patients of reproductive potential should be verified prior to initiating Evrysdi therapy. Pregnant women should be clearly advised of the potential risk to the foetus.

Pregnancy

There are no data from the use of Evrysdi in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).
Evrysdi is not recommended during pregnancy and in women of childbearing potential not using contraception (see section 4.4).

Breast-feeding

It is not known whether risdiplam is excreted in human breast milk. Studies in rats show that risdiplam is excreted into milk (see section 5.3). As the potential for harm to the breastfed infant is unknown, it is recommended not to breastfeed during treatment.

Fertility

Male patients

Male fertility may be compromised while on treatment, based on nonclinical findings. In rat and monkey reproductive organs, sperm degeneration and reduced sperm numbers were observed (see section 5.3). Based on observations from animal studies, the effects on sperm cells are expected to be reversible upon discontinuation of risdiplam.

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 for a minimum of 4 months. Treatment may be re-started after conception.

Female patients

Based on nonclinical data (see section 5.3), an impact of risdiplam on female fertility is not expected.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

In infantile-onset SMA patients, the most common adverse reactions observed in Evrysdi clinical studies were pyrexia (54.8%), rash (29.0%) and diarrhoea (19.4%).

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

The adverse reactions listed above occurred without an identifiable clinical or time pattern and generally resolved despite ongoing treatment in infantile-onset and later-onset SMA patients.

Based on the primary analysis of RAINBOWFISH, the safety profile of Evrysdi in pre-symptomatic patients is consistent with the safety profile of symptomatic infantile-onset and later-onset SMA patients. The RAINBOWFISH study enrolled 26 patients with pre-symptomatic SMA between 16 and 41 days of age at the time of the first dose (weight range 3.1 to 5.7 kg). The median exposure duration

was 20.4 months (range: 10.6 to 41.9 months). Limited post-marketing data are available in neonates <20 days of age.

See also section 5.3 for the effects of Evrysdi observed in nonclinical studies.

Tabulated list of adverse reactions

The corresponding frequency category 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). Adverse drug reactions from clinical studies (Table 2) are listed by MedDRA system organ class.

Table 2. Adverse drug reactions occurring in patients with infantile-onset and later-onset SMA based on Evrysdi clinical studies

System Organ Class	Infantile-onset SMA (Type 1)	Later-onset SMA (Type 2 and 3)
Gastrointestinal disorders		
Diarrhoea	Very common	Very common
Nausea	Not applicable	Common
Mouth ulcerations and aphthous ulcers	Common	Common
Skin and subcutaneous tissue disorders		
Rash*	Very common	Very common
Nervous system disorders		
Headache	Not applicable	Very common
General disorders and administration site conditions		
Pyrexia (including hyperpyrexia)	Very common	Very common
Infections and infestations		
Urinary tract infection (including cystitis)	Common	Common
Musculoskeletal and connective tissue disorders		
Arthralgia	Not applicable	Common

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

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 SMA treatment non-naive patients who received Evrysdi for up to 59 months (including those previously treated with nusinersen [n=76] or with onasemnogene abeparvovec [n=14]) is consistent with the safety profile in SMA treatment-naive patients treated with Evrysdi in the FIREFISH, SUNFISH and RAINBOWFISH studies (see section 5.1).

Post-marketing experience

Cutaneous vasculitis was reported during post-marketing experience. Symptoms recovered after permanent discontinuation of Evrysdi. The frequency cannot be estimated based on available data.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/

4.9 Overdose

There is no known antidote for overdosage of Evrysdi. In the event of an overdose, the patient should be closely supervised and supportive care instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Risdiplam is a survival of motor neuron 2 (*SMN2*) pre-mRNA splicing modifier designed to treat SMA caused by mutations of the *SMN1* gene in chromosome 5q that lead to SMN protein deficiency. Functional SMN protein deficiency is directly linked to the SMA pathophysiology which includes progressive loss of motor neurons and muscle weakness. 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 of functional and stable SMN protein. Thus, risdiplam treats SMA by increasing and sustaining functional SMN protein levels.

Pharmacodynamic effects

In the studies FIREFISH (patients aged 2-7 months at enrolment), SUNFISH (patients aged 2-25 years at enrolment), and JEWELFISH (patients aged 1-60 years at enrolment) in infantile-onset SMA and later-onset SMA patients, risdiplam led to an increase in SMN protein in blood with a greater than 2-fold median change from baseline within 4 weeks of treatment initiation across all SMA types studied. The increase was sustained throughout the treatment period (of at least 24 months).
Cardiac electrophysiology

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.

Clinical efficacy and safety

The efficacy of Evrysdi for the treatment of SMA patients with infantile-onset (SMA Type 1) and later-onset SMA (SMA type 2 and 3) was evaluated in 2 pivotal clinical studies, FIREFISH and SUNFISH. Efficacy data of Evrysdi for the treatment of pre-symptomatic SMA patients was evaluated in the RAINBOWFISH clinical study. Patients with a clinical diagnosis of Type 4 SMA have not been studied in clinical trials.

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 a dose-finding part of the study. The confirmatory Part 2 of the FIREFISH study assessed the efficacy of Evrysdi. Patients from Part 1 did not take part in Part 2.

The key efficacy endpoint was the ability to sit without support for at least 5 seconds, as measured by Item 22 of the Bayley Scales of Infant and Toddler Development – Third Edition (BSID-III) gross motor scale, after 12 months of treatment.

FIREFISH Part 2

In FIREFISH Part 2, 41 patients with Type 1 SMA were enrolled. The median age of onset of clinical signs and symptoms of Type 1 SMA was 1.5 months (range: 1.0-3.0 months), 54% were female, 54% Caucasian and 34% Asian. The median age at enrolment was 5.3 months (range: 2.2-6.9 months) and the median time between onset of symptoms and first dose was 3.4 months (range: 1.0-6.0 months). At baseline, the median Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP-INTEND) score was 22.0 points (range: 8.0-37.0) and the median Hammersmith Infant Neurological Examination Module 2 (HINE-2) score was 1.0 (range: 0.0-5.0).

The primary endpoint was the proportion of patients with the ability to sit without support for at least 5 seconds after 12 months of treatment (BSID-III gross motor scale, Item 22). The key efficacy endpoints of Evrysdi treated patients are shown in Table 3.

Table 3. Summary of key efficacy results at month 12 and month 24 (FIREFISH Part 2)

Efficacy Endpoints	Proportion of Patients N=41 (90% CI)	
	Month 12	Month 24
Motor function and development milestones		
BSID-III: sitting without support for at least 5 seconds	29.3% (17.8%, 43.1%) p <0.0001[a]	61.0% (46.9%, 73.8%)
CHOP-INTEND: score of 40 or higher	56.1% (42.1%, 69.4%)	75.6% (62.2%, 86.1%)
CHOP-INTEND: increase of ≥4 points from baseline	90.2% (79.1%, 96.6%)	90.2% (79.1%, 96.6%)
HINE-2: motor milestone responders[b]	78.0% (64.8%, 88.0%)	85.4% (73.2%, 93.4%)
HINE-2: sitting without support[c]	24.4% (13.9%, 37.9%)	53.7% (39.8%, 67.1%)
Survival and event-free survival		
Event-free survival[d]	85.4% (73.4%, 92.2%)	82.9% (70.5%, 90.4%)
Alive	92.7% (82.2%, 97.1%)	92.7% (82.2%, 97.1%)
Feeding		
Ability to feed orally[e]	82.9% (70.3%, 91.7%)	85.4% (73.2%, 93.4%)

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

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

[b] According to HINE-2: ≥2 point increase [or maximal score] in ability to kick, OR ≥1 point increase in the motor milestones of head control, rolling, sitting, crawling, standing or walking, AND improvement in more categories of motor milestones than worsening is defined as a responder for this analysis.

[c] Sitting without support includes patients that achieved "stable sit" (24%, 10/41) and "pivots (rotates)" (29%, 12/41) as assessed by the HINE-2 at Month 24.

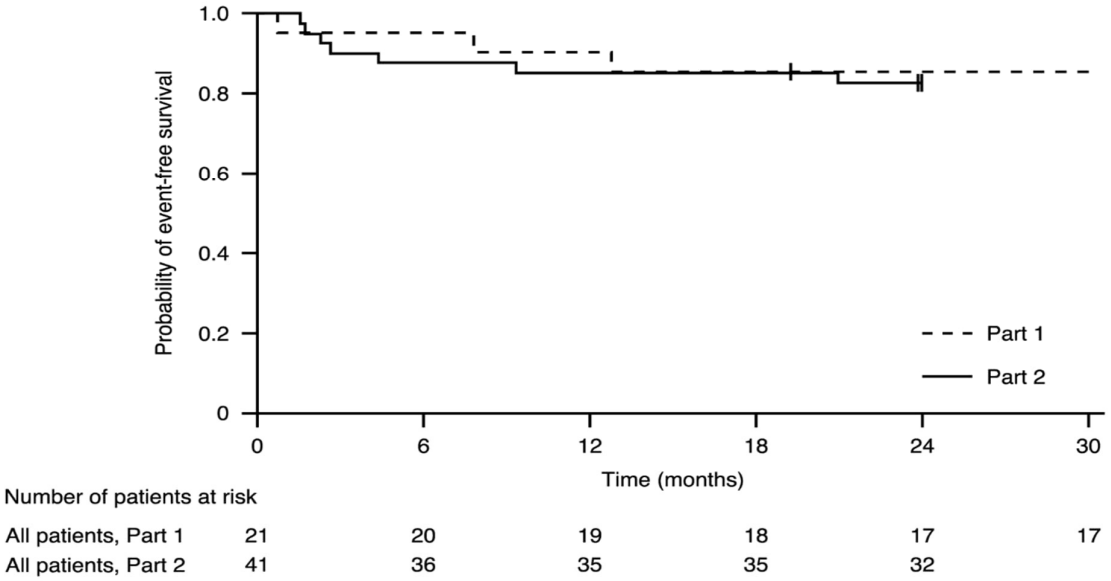
[d] An event is meeting the endpoint of permanent ventilation defined as tracheostomy or ≥16 hours of non-invasive ventilation per day or intubation for > 21 consecutive days in the absence of, or following the resolution of, an acute reversible event. Three patients died within the first 3 months following study enrolment and 4 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.

[e] Includes patients who were fed exclusively orally (29 patients overall) and those who were fed orally in combination with a feeding tube (6 patients overall) at Month 24.

At Month 24, 44% of patients achieved sitting without support for 30 seconds (BSID-III, Item 26). Patients continued to achieve additional motor milestones as measured by the HINE-2; 80.5% were able to roll and 27% of patients achieved a standing measure (12% supporting weight and 15% standing with support).

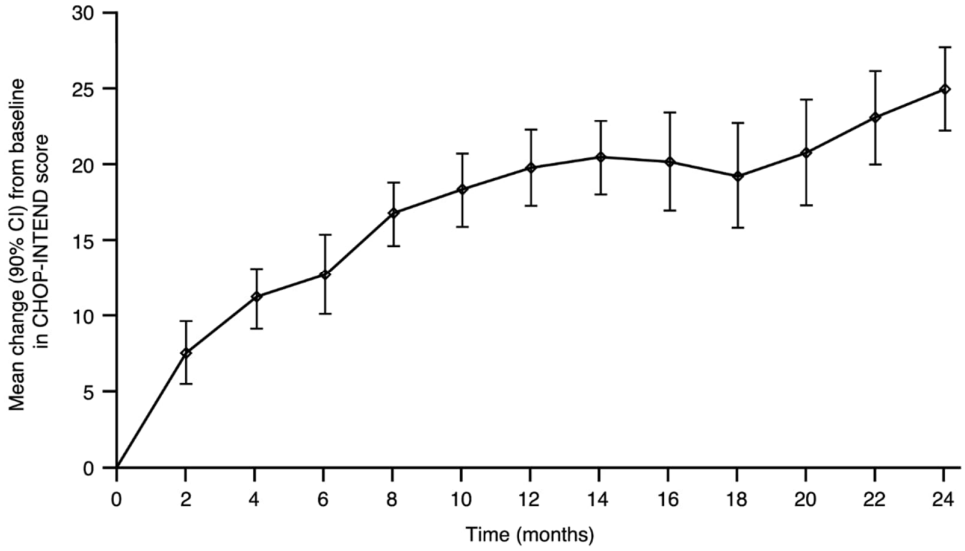
Untreated patients with infantile-onset SMA would never be able to sit without support and only 25% would be expected to survive without permanent ventilation beyond 14 months of age.

Figure 1. Kaplan-Meier plot of event-free survival (FIREFISH Part 1 and Part 2)



+ Censored: two patients in Part 2 were censored because the patients attended the Month 24 visit early, one patient in Part 1 was censored after discontinuing treatment and died 3.5 months later

Figure 2. Mean change from baseline in CHOP-INTEND total score (FIREFISH Part 2)



FIREFISH Part 1

The efficacy of Evrysdi in Type 1 SMA patients is also supported by results from FIREFISH Part 1. For the 21 patients from Part 1, the baseline characteristics were consistent with symptomatic patients with Type 1 SMA. The median age at enrolment was 6.7 months (range: 3.3-6.9 months) and the median time between onset of symptoms and first dose was 4.0 months (range: 2.0-5.8 months).

A total of 17 patients received the therapeutic dose of Evrysdi (dose selected for Part 2). After 12 months of treatment, 41% (7/17) of these patients were able to sit independently for at least 5 seconds (BSID-III, Item 22). After 24 months of treatment, 3 more patients receiving the therapeutic dose were able to sit independently for at least 5 seconds, leading to a total of 10 patients (59%) achieving this motor milestone.

After 12 months of treatment, 90% (19/21) of patients were alive and event-free (without permanent ventilation) and reached 15 months of age or older. After a minimum of 33 months of treatment, 81% (17/21) of patients were alive and event-free and reached an age of 37 months or older (median 41 months; range 37 to 53 months), see Figure 1. Three patients died during treatment and one patient died 3.5 months after discontinuing treatment.

Later Onset SMA

Study BP39055 (SUNFISH), is a 2-part, multicentre study 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 exploratory dose-finding portion and Part 2 was the randomized, double-blind, placebo-controlled confirmatory portion. Patients from Part 1 did not take part in Part 2.

The primary endpoint was the change from baseline score at Month 12 on the Motor Function Measure-32 (MFM32). The MFM32 has the ability to assess a wide range of motor function across a broad range of SMA patients. The total MFM32 score is expressed as a percentage (range: 0-100) of the maximum possible score, with higher scores indicating greater motor function.

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 4.2) 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. Overall, 30% were 2 to 5 years of age, 32% were 6 to 11 years of age, 26% were 12-17 years of age, and 12% were 18 to 25 years of age at study enrolment. Of the 180 patients included in the study, 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 baseline demographic characteristics were balanced between Evrysdi and placebo arms with the exception of scoliosis (63% of patients in the Evrysdi arm and 73% 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 4, Figure 3, and Figure 4.

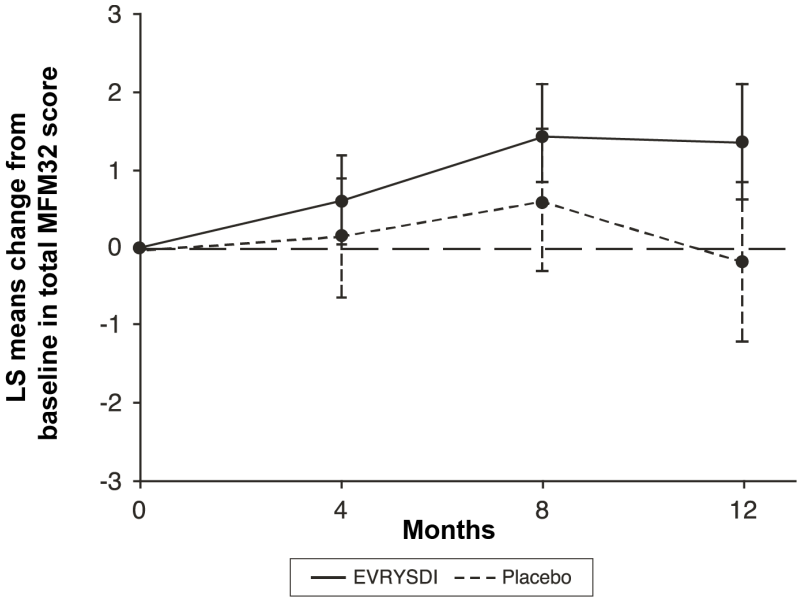
Table 4. Summary of efficacy in patients with later-onset SMA at month 12 of treatment (SUNFISH Part 2)

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)[1]	38.3% (28.9, 47.6)	23.7% (12.0, 35.4)
Odds ratio for overall response (95% CI) Adjusted(unadjusted) p-value[3,4]	2.35 (1.01, 5.44) 0.0469 (0.0469)	
Change from baseline in RULM total score[5] at Month 12 LS mean (95% CI)	1.61 (1.00, 2.22)	0.02 (-0.83, 0.87)
Difference from placebo estimate (95% CI) Adjusted (unadjusted) p-value[2,4]	1.59 (0.55, 2.62) 0.0469 (0.0028)	

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

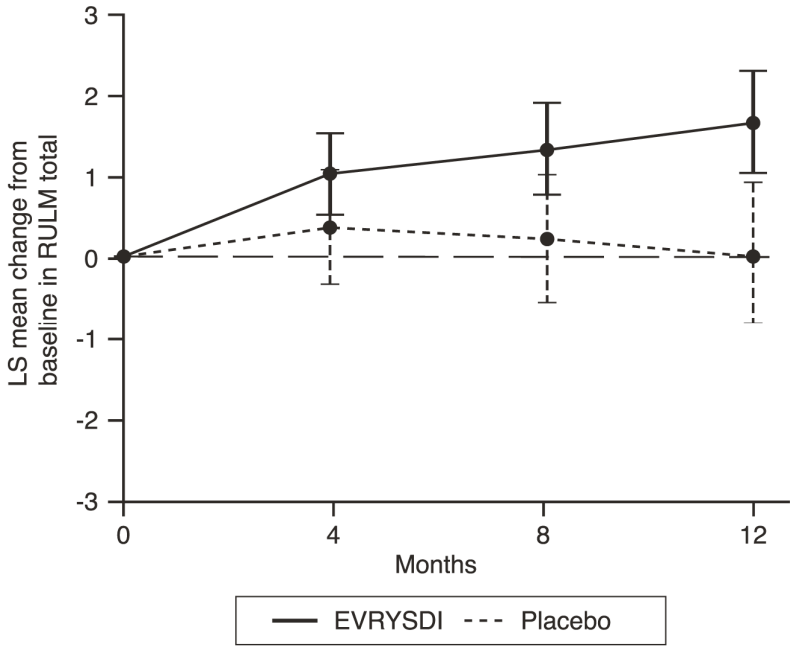
Upon completion of 12 months of treatment, 117 patients continued to receive Evrysdi. At the time of the 24 month analysis, these patients who were treated with Evrysdi for 24 months overall experienced maintenance of improvement in motor function between month 12 and month 24. The mean change from baseline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

Figure 3. Mean change from baseline in MFM32 total 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 RULM total 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]

SUNFISH Part 1

Efficacy 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 of age were enrolled. After 1 year of treatment there was a clinically meaningful improvement in motor function as measured by MFM32, with a mean change from baseline of 2.7 points (95% CI: 1.5, 3.8). The improvement in MFM32 was maintained up to 2 years on treatment (mean change of 2.7 points [95% CI: 1.2, 4.2]).

Use in patients previously treated with other SMA-modifying therapies (JEWELFISH)

Study BP39054 (JEWELFISH, n = 174) 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 (median age 14 years [range 1 - 60 years]), who had previously received treatment with other approved (nusinersen n = 76, onasemnogene abeparvovec n = 14) or investigational SMA modifying therapies. At baseline, out of the 168 patients aged 2 - 60 years, 83% of patients had scoliosis and 63% had a Hammersmith Functional Motor Scale Expanded (HFMSE) score < 10 points.

At the analysis at month 24 of treatment, patients 2 - 60 years of age showed overall stabilization in motor function in MFM-32 and RULM (n = 137 and n = 133, respectively). Patients less than 2 years (n = 6) maintained or gained motor milestones such as head control, rolling and sitting independently. All ambulatory patients (aged 5 - 46 years, n = 15) retained their ability to walk.

Pre-symptomatic SMA (RAINBOWFISH)

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] treated with Evrysdi: eight patients, 13 patients, and 5 patients had 2, 3, and ≥4 copies of the *SMN2* gene, respectively. The median age of these patients at first dose was 25 days (range: 16 to 41 days), 62% were female, and 85% were Caucasian. 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 5 and 6, and in Figure 5.

Table 5. 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 6. 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 hospitalisations[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

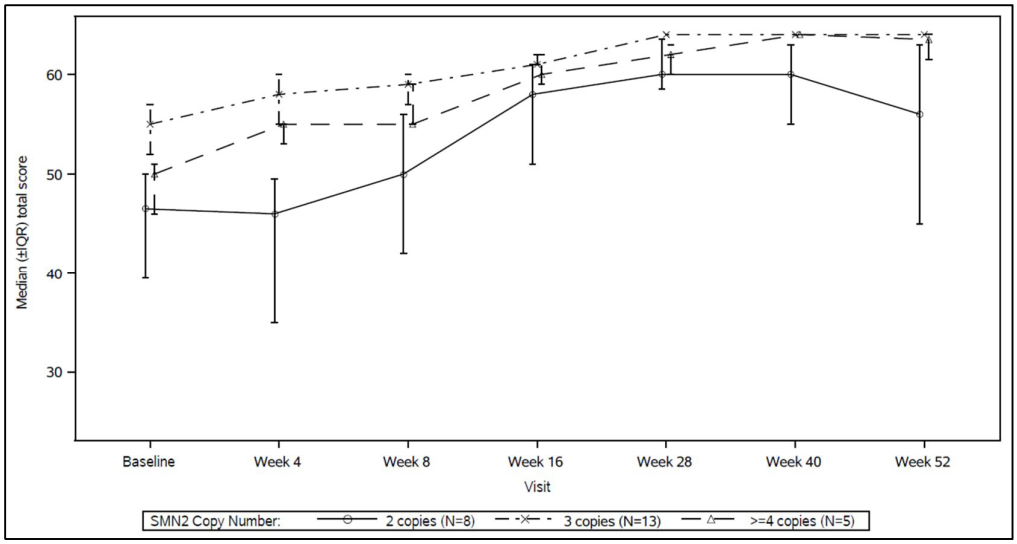
[a] Based on N=25

[b] One patient was not assessed.

[c] Hospitalisations include all hospital admissions which spanned at least two days, and which are not due to study requirements.

[d] An event refers to death or permanent ventilation; permanent ventilation is defined as tracheostomy or ≥16 hours of non-invasive ventilation per day or intubation for > 21 consecutive days in the absence of, or following the resolution of, an acute reversible event.

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



Abbreviations: IQR = Interquartile range; SMN2 = Survival of Motor Neuron 2.

5.2 Pharmacokinetic properties

Pharmacokinetic parameters have been characterised in healthy adult subjects and in patients with SMA.

After administration of treatment 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 enrolment) at the therapeutic dose of 0.2 mg/kg once daily was 1930 ng.h/mL. The estimated mean exposure in pre-symptomatic infants (16 days to <2 months of age) in the RAINBOWFISH study was 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 enrolment) in the SUNFISH (Part 2) study 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 estimated exposure (mean $AUC_{0\text{-}24h}$) for SMA treatment non-naïve patients (age 1-60 years at enrolment) was 1700 ng.h/mL at the therapeutic dose of 0.25 mg/kg or 5 mg. The observed maximum concentration (mean C_{max}) was 194 ng/mL at 0.2 mg/kg in FIREFISH, 120 ng/mL in SUNFISH Part 2 , 129 ng/mL in JEWELFISH, and the estimated maximum concentration at 0.15 mg/kg in RAINBOWFISH is 111 ng/mL.

Absorption

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

Distribution

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.

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%.

Biotransformation

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

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

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.

Pharmacokinetics in special populations

Paediatric population
Body weight and age were identified as covariates in the population PK analysis. On the basis of such model, 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. Limited PK data are available in patients less than 20 days of age , since only one 16-day-old neonate received risdiplam at a lower dose (0.04 mg/kg) in clinical studies.

No data on risdiplam pharmacokinetics are available in patients less than 16 days of age

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

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

Hepatic impairment
Mild and moderate hepatic impairment had no significant impact on the PK of risdiplam. After a single oral 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.

5.3 Preclinical safety data

Impairment of fertility

Treatment with risdiplam was associated with male germ cell arrest in rats and monkeys without safety margins based on systemic exposures at the no observed adverse effect level (NOAEL). These effects led to degenerated spermatocytes, degeneration/necrosis of the seminiferous epithelium, and oligo/aspermia in the epididymis. Sperm cell effects of risdiplam are likely related to an interference of risdiplam with the cell cycle of dividing cells, which is stage specific and expected to be reversible. No effects were seen on female reproductive organs in rats and monkeys after treatment with risdiplam.

No fertility and early embryonic development studies were conducted with concomitant administration of risdiplam, as sperm cell arrest and embryotoxic potential under treatment was already identified with treatment of rats and monkeys in other toxicity studies. No impairment on male fertility or female fertility was observed in two studies in which rats were mated, either following completion of a 13-week treatment period starting at weaning, or 8 weeks after completion of a 4-week treatment period starting at 4 days of age.

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 by electroretinography (ERG). Effects were seen with exposures in excess of 2-fold the exposure in humans at the therapeutic dose without safety margin based on systemic exposures at the NOAEL. 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 gastro intestinal 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-fold the average exposure in humans at the therapeutic dose.

Effect on haematological 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 longer treatment of rats for 26 weeks, the exposure margins to the NOAEL were approximately 4-fold the average exposure in humans at the therapeutic dose.

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 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. Risdiplam does not possess a potential to damage DNA directly.

Reproductive toxicity

In studies in pregnant rats treated with risdiplam, embryofoetal toxicity with lower fetal weight and delayed development was evident. The NOAEL for this effect was approximately 2-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 4-fold the exposure levels reached at the therapeutic dose of risdiplam in patients. In a pre- and post-natal development study in rats treated daily with risdiplam, risdiplam caused a slight delay in gestation length. Studies in pregnant and lactating rats showed that risdiplam crosses the placental barrier and is excreted into milk.

Carcinogenicity

Risdiplam did not reveal a carcinogenic potential in transgenic rasH2 mice over 6 months and in a 2 year study in rats at equivalent exposures to those in humans receiving the maximum recommended human dose (MRHD). Significantly increased tumours of the preputial gland in male rats and clitoral gland in female rats at 4 times the exposure of the MRHD are without human relevance, because both are rodent-specific organs.

Juvenile animal studies

Juvenile animal data reveal no special hazard for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

mannitol
isomalt
strawberry flavour
tartaric acid
sodium benzoate
macrogol/polyethylene glycol 6000
sucralose
ascorbic acid
disodium edetate dihydrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Powder for oral solution
The expiry date of the product is indicated on the packaging materials

Constituted oral solution
64 days stored in a refrigerator (2 to 8°C). Do not freeze.

If necessary, the patient or their caregiver may store the oral solution at room temperature (below 40˚C) for no more than a total of 120 hours (5 days). The oral solution should be returned to the refrigerator when it is no longer necessary to keep the bottle at room temperature. The total time outside the refrigerator (below 40˚C) should be monitored.

The oral solution should be discarded if it has been stored at room temperature (below 40°C) for more than a total of 120 hours (5 days), or for any period of time kept above 40°C

6.4 Special precautions for storage

Powder for oral solution

Do not store above 25^0C. Keep in the original amber glass bottle to protect from light.

Constituted oral solution

For storage conditions after constitution of the medicinal product, see section 6.3.
Keep the oral solution in the original amber glass bottle to protect from light and keep the bottle always in an upright position with the cap tightly closed.

6.5 Nature and contents of container

Amber type III glass bottle with a tamper-evident child resistant screw cap.

Each carton contains; one bottle, 1 press-in bottle adaptor, two re-usable 1 mL, two re-usable 6 mL and one re-usable 12 mL graduated amber oral syringes.

6.6 Special precautions for disposal and other handling

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

Preparation

Caution should be exercised in the handling of Evrysdi powder for oral solution (see section 4.4). Avoid inhalation and direct contact with skin or mucous membranes with the dry powder and the constituted solution.

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

Instructions for constitution:

1. Gently tap the bottom of the closed glass bottle to loosen the powder.
2. Remove the cap. Do not throw away the cap.
3. Carefully pour 79 mL of purified water or water for injection into the Evrysdi bottle to yield the 0.75 mg/mL oral solution.
4. Hold the medicine bottle on the table with one hand. Insert the press-in bottle adaptor into the opening by pushing it down with the other hand. Ensure the adaptor is completely pressed against the bottle lip.
5. Put the cap back on the bottle and close the bottle tightly. Ensure it is completely closed and then shake well for 15 seconds. Wait for 10 minutes. You should have obtained a clear solution. Afterwards, shake well again for another 15 seconds.
6. Write the “Discard after” date of the solution on the bottle label and carton. (The “Discard after” date is calculated as 64 days after constitution, the day of constitution is counted as day 0). Put the bottle back in its original carton with syringes (in pouches), Package Leaflet, and Instructions for Use booklet. Store the carton in the refrigerator (2 to 8°C).

Discard any unused portion 64 days after constitution.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Pharmaceuticals (Israel) Ltd., P.O.Box 6391 Hod Hasharon 4524079.

8. MARKETING AUTHORISATION NUMBER(S)

167-71-36630-99

9. MANUFACTURER

F. Hoffmann-La Roche Ltd., Switzerland
Grenzacherstrasse 124, Ch-4070, Basel, Switzerland

Revised in May 2024