# NEW ZEALAND DATA SHEET
# Evrysdi® (risdiplam) powder for oral solution

## 1. PRODUCT NAME

Evrysdi (risdiplam) 750 microgram/mL powder for oral solution

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bottle of Evrysdi is filled with 2.0 g of powder containing 60 mg of risdiplam. The powder is reconstituted to form an oral solution containing risdiplam 750 microgram/mL.

Excipients with known effect

Evrysdi contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'. For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder for oral solution.

Evrysdi is supplied as a powder in an amber glass bottle.

The powder is reconstituted with purified water or water for injections to yield an oral solution containing 750 microgram/mL of risdiplam (see section 6.6 Preparation of the powder for oral solution by a healthcare professional).

## 4. CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

Evrysdi is indicated for the treatment of spinal muscular atrophy (SMA) in patients aged 2 months and older.

### 4.2 DOSE AND METHOD OF ADMINISTRATION

Evrysdi oral solution must be reconstituted by a healthcare professional prior to being dispensed (see section 6.6 Preparation of the powder for oral solution by a healthcare professional). The reconstituted solution appears greenish yellow to yellow in colour.

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

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

In infants who are breastfed, Evrysdi should be administered after breastfeeding. Evrysdi cannot be mixed with formula or milk.

**Dose**

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

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

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

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

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.

Special populations

*Hepatic impairment*

No dose adjustment is required in patients with mild or moderate hepatic impairment (see section 5.2 Pharmacokinetics in special populations, Hepatic impairment). Evrysdi has not been studied in patients with severe hepatic impairment.

*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 section 5.2 Pharmacokinetics in special populations, Renal impairment).

*Elderly*

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 section 5.2 Pharmacokinetics in special populations, Elderly).

*Paediatric populations*

The safety and efficacy of Evrysdi in paediatric patients < 2 months of age have not yet been established (see section 5.1 Clinical trials).

**Method of administration**

For instructions on reconstitution of the medicine before administration, see section 6.6 Preparation of the powder for oral solution by a healthcare professional.

Use the re-usable oral syringe provided to deliver the daily dose of Evrysdi. It is recommended that a healthcare professional discuss with the patient or caregiver how to prepare the prescribed daily dose prior to administration of the first dose.

For the calculation of dosing volume, the syringe markings need to be considered. Round up or round down the dose volume to the nearest graduation mark on the selected oral syringe (see Table 2).

**Table 2 Selecting the Oral Syringe for the Prescribed Daily Dose of Evrysdi**

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

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.

The patient should drink water after taking Evrysdi to ensure the medicine 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.

Refer to the "Instructions for Use – Administration" provided in the pack.

## 4.3 CONTRAINDICATIONS

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

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

**Embryo-fetal toxicity**

Embryo-fetal toxicity has been observed in animal studies (see section 5.3 Reproductive toxicity). Patients of reproductive potential should be informed of the risks and must use highly effective contraception during treatment and until at least 1 month after the last dose of Evrysdi in female patients, and 4 months after the last dose of Evrysdi in male patients (see section 4.6 Contraception in males and females).

**Potential effects on male fertility**

Male patients should not donate sperm while on treatment and for 4 months after the last dose of Evrysdi due to reversible effects of Evrysdi on male fertility, based on observations from animal studies (see section 4.6 Effects on fertility).

**Use in 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 4.2 Dose, Special populations, Hepatic impairment and 5.2 Pharmacokinetics in special populations, Hepatic impairment).

**Use in 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 4.2 Dose, Special populations, Renal impairment and 5.2 Pharmacokinetics in special populations, Renal impairment).

**Use in the elderly**

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 4.2 Dose, Special populations, Elderly and 5.2 Pharmacokinetics in special populations, Elderly).

**Paediatric use**

The safety and efficacy of Evrysdi have been established in paediatric patients ≥ 2 months old (see section 5.1 Clinical trials).

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

**Effects of other medicines on Evrysdi**

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

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

**Effects of Evrysdi on other medicines**

*In vitro* risdiplam and its major circulating metabolite M1 did not induce CYP1A2, 2B6, 2C8, 2C9, 2C19 or 3A4. *In vitro* risdiplam and M1 did not inhibit (reversible or Time-Dependent Inhibition) any of the CYP enzymes tested (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6) with the exception of CYP3A.

Evrysdi is a weak inhibitor of CYP3A. In healthy adult subjects, administration of Evrysdi once daily for 2 weeks slightly increased the exposure of midazolam, a sensitive CYP3A substrate (AUC 11%; $C_{max}$ 16%). The extent of the interaction is not considered clinically relevant and therefore no dose adjustment is required for CYP3A substrates. Based on physiologically based pharmacokinetic (PBPK) modelling, a similar magnitude of the effect is expected in children and infants as young as 2 months old.

*In vitro* studies have shown that risdiplam and its major metabolite are not significant inhibitors of human MDR1, organic anion-transporting polypeptide (OATP)1B1, OATP1B3, organic anion transporter 1 and 3 (OAT 1 and 3). Risdiplam and its metabolite are, however, *in vitro* inhibitors of the human organic cation transporter 2 (OCT2) and the multidrug and toxin extrusion (MATE)1 and MATE2-K transporters. At therapeutic drug concentrations, no interaction is expected with OCT2 substrates. Based on *in vitro* data, Evrysdi may increase plasma concentrations of drugs eliminated via MATE1 or MATE2-K. The clinical relevance of the co-administration with MATE1/2-K substrates is unknown.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

### Fertility

Male patients

Based on nonclinical findings, male fertility may be compromised while on treatment with Evrysdi. In rat and monkey reproductive organs, sperm degeneration and reduced sperm numbers were observed (see section 5.3 Impairment of fertility). The effects on sperm cells are reversible upon discontinuation of Evrysdi.

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 5.3 Impairment of fertility).

### Patients of reproductive potential

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 in males and females

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.

**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 5.3 Reproductive toxicity).

Evrysdi should not be used during pregnancy unless the benefit to the mother outweighs the potential risks to the fetus. If a pregnant woman needs to be treated with Evrysdi, she should be clearly advised on the potential risk to the fetus.

Labour and delivery

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

**Breastfeeding**

It is not known whether Evrysdi is excreted in human breast milk. Studies in rats show that risdiplam is excreted into milk (see section 5.3 Reproductive toxicity). As the potential for harm to the nursing infant is unknown, a decision must be made with the treating physician. It is recommended not to breastfeed during treatment with Evrysdi.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

## 4.8 UNDESIRABLE EFFECTS

**Summary of the safety profile**

The safety profile of Evrysdi is based on three clinical trials FIREFISH, SUNFISH, and JEWELFISH (see section 5.1 Clinical trials).

The safety profile for infantile-onset SMA patients is based on the pooled analysis of 62 patients from the FIREFISH study Part 1 and 2. FIREFISH 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). The adverse drug reactions (ADRs) observed in clinical trials for infantile-onset SMA are based on the pooled analysis of patients from FIREFISH Part 1 and 2 (see Table 3). ADRs are defined as adverse events occurring in ≥ 5% of patients and where a causal association with Evrysdi is possible.

The safety profile for later-onset SMA patients is based on the SUNFISH Part 2 study. The SUNFISH study is a two-part study with later-onset SMA between 2-25 years of age. The ADRs observed in clinical trials for later-onset SMA are based on SUNFISH Part 2 (n=180), the randomised double-blind, placebo-controlled portion of the study with a follow-up duration of at least 12 months (see Table 4). ADRs are defined as adverse events occurring in ≥ 5% of Evrysdi treated patients which occurred ≥ 5% more frequently, or at least 2-times as

frequently, as in placebo control patients and where a causal association with Evrysdi is possible.

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 5.3 Effect on epithelial tissues).

Safety profile in patients treated previously for SMA

In the JEWELFISH study, 76 patients previously treated with nusinersen and 14 patients previously treated with onasemnogene abeparvovec were enrolled. The safety profile of Evrysdi in the treatment of non-treatment naive patients in the JEWELFISH study is consistent with the safety profile for treatment naive SMA patients treated with Evrysdi in the FIREFISH and SUNFISH studies.

**Tabulated summary of adverse reactions**

Tables 3 and 4 summarise the adverse reactions that have been reported in association with the use of Evrysdi in FIREFISH Part 1 and 2 and SUNFISH Part 2.

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 trials are listed by MedDRA system organ class.

**Table 3 Summary of adverse drug reactions for infantile-onset SMA patients observed in the FIREFISH study (Parts 1 and 2)**

| **System Organ Class**<br>Adverse Drug Reaction | **Incidence**<br>N=62<br>n (%) | **Number of events/ 100 patient years**<br>(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

**Table 4 Summary of adverse drug reactions for later-onset SMA patients observed in Part 2 of the SUNFISH study**

| **System Organ Class**<br>Adverse Drug Reaction | **Evrysdi**<br>N=120<br>n (%) | **Placebo**<br>N=60<br>n (%) | **Frequency Category** |
|---|---|---|---|
| **Gastrointestinal disorders** | | | |
| Diarrhoea | 20 (16.7) | 5 (8.3) | Very common |
| **Skin and Subcutaneous Tissue Disorders** | | | |

| | | | |
|---|---|---|---|
| Rash* | 20 (16.7) | 1 (1.7) | Very common |

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

**Post-marketing experience**

The following adverse drug reaction has been identified from postmarketing experience with Evrysdi (Table 5). Adverse drug reaction is listed according to system organ classes in MedDRA.

**Table 5 Adverse drug reactions from post-marketing experience**

| System Organ Class | Adverse Reaction | Frequency Category |
|---|---|---|
| Skin and Subcutaneous Disorders | Cutaneous vasculitis[1] | Unknown |

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

Cutaneous vasculitis was identified during post-marketing experience. Symptoms recovered after permanent discontinuation of Evrysdi.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

## 4.9 OVERDOSE

There is no experience with overdose of Evrysdi in clinical trials. There is no known antidote for overdose of Evrysdi. In case of overdose, the patient should be closely supervised and supportive care instituted.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 PHARMACODYNAMIC PROPERTIES

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

**Mechanism of action**

Evrysdi 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. Evrysdi 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, Evrysdi 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 all clinical trials, Evrysdi 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 up to 2 years for infantile-onset SMA and later-onset SMA patients (see section 5.1 Clinical trials).

**Clinical trials**

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 is supported by additional data from the JEWELFISH study. The overall findings of these studies support the effectiveness of Evrysdi for SMA patients.

Infantile-onset SMA

Study BP39056 (FIREFISH) is an open-label, 2-part study to investigate the efficacy, safety, PK and pharmacodynamics (PD) of Evrysdi in symptomatic Type 1 SMA patients (all patients had genetically confirmed disease with 2 copies of the SMN2 gene). Part 1 of FIREFISH was designed as the dose-finding part of the study. The confirmatory Part 2 of the FIREFISH study assessed the efficacy of Evrysdi at the therapeutic dose selected based on the results from Part 1 (see section 4.2 Dose and method of administration). Patients from Part 1 did not take part in Part 2.

A total of 62 patients with symptomatic Type 1 SMA were enrolled in FIREFISH Part 1 (n=21) and Part 2 (n=41), of which 58 patients received the therapeutic dose. The median age of onset of clinical signs and symptom was 1.5 months (range: 0.9 to 3.0 months). The median age at enrolment was 5.6 months (range: 2.2 to 6.9 months), and the median time between onset of symptoms and the first dose was 3.7 months (range 1.0 to 6.0 months). Of these patients, 60% were female, 57% were Caucasian, and 29% were Asian. At baseline the median CHOP-INTEND score was 23 (range: 8 to 37), and the median HINE-2 score was 1 (range: 0 to 5). The baseline demographics and disease characteristics of those enrolled in Part 1 were comparable to those in Part 2.

The primary endpoint was the proportion of patients with the ability to sit without support for at least 5 seconds (BSID-III gross motor scale, Item 22) after 12 months of treatment in Part 2; 29% of patients (n=12/41, 90% CI: 17.8%, 43.1%, p <0.0001) achieved this milestone.

The key efficacy endpoints of Evrysdi treated patients in FIREFISH Part 1 and Part 2 are shown in Table 6, and displayed in Figure 1 and Figure 2.

**Table 6:** 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 Utilisation | | |
| No hospitalisations[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 utilisation 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] Hospitalisations include all hospital admissions which spanned at least two days.

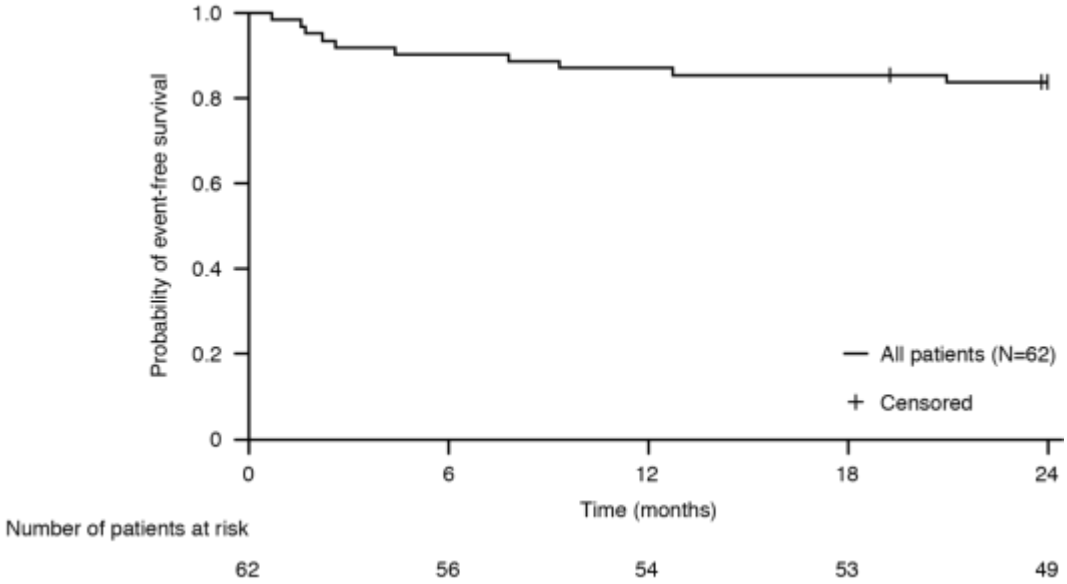
[e] An event is meeting the endpoint of permanent ventilation defined as tracheostomy or ≥16 hours of non-invasive ventilation per day or intubation for > 21 consecutive days in the absence of, or following the resolution of, an acute reversible event. Four patients met the endpoint of permanent ventilation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

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

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

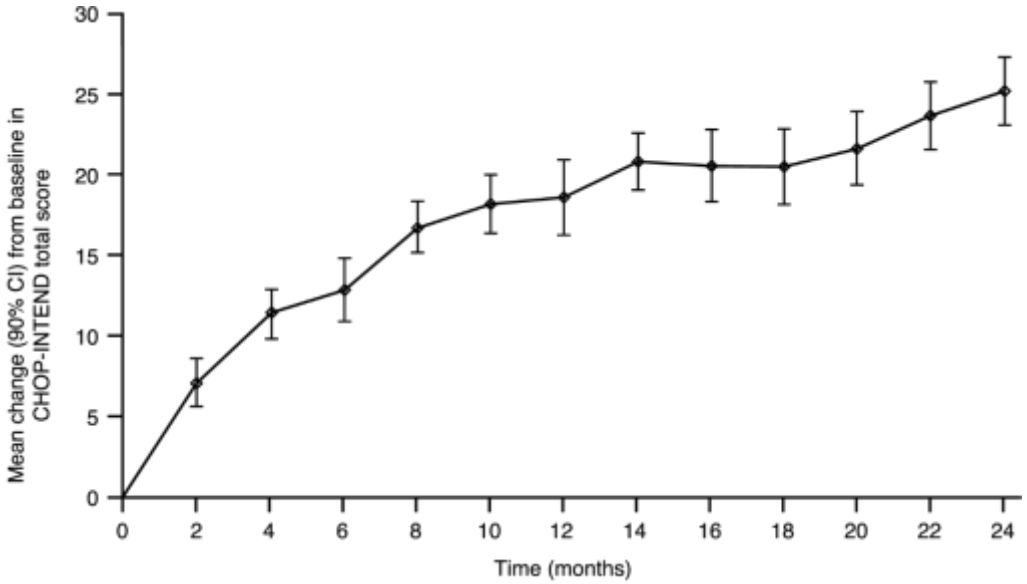
These results indicate a clinically meaningful deviation from the natural history of untreated infantile-onset SMA. Untreated patients with infantile-onset SMA would never be able to sit without support and only 25% would be expected to survive without permanent ventilation beyond 14 months of age.

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




+ Censored: two patients were censored because they attended the Month 24 visit early, 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 2)**



Later-onset SMA

Study BP39055 (SUNFISH), is a 2-part, multicentre 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 randomised, 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 randomised, double-blind, placebo-controlled portion of the SUNFISH study in 180 non-ambulant patients with Type 2 (71%) or Type 3 (29%) SMA. Patients were randomised 2:1 to receive either Evrysdi at the therapeutic dose (see section 4.2 Dose and method of administration) or placebo. Randomisation 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) and 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 a 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 7 and Figures 3 and 4.

**Table 7 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)<br>Adjusted (unadjusted) p-value[3,4] | 2.35 (1.01, 5.44)<br>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)<br>0.0469 (0.0028) | |

Abbreviations: MFM32=Motor Function Measure-32; LS=least squares; CI=confidence interval; RULM= Revised Upper Limb Module

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.

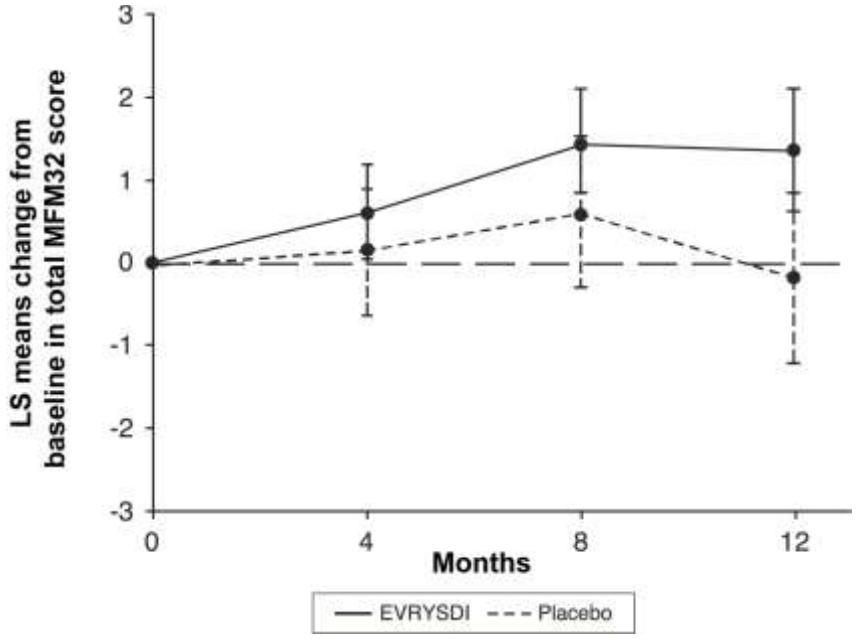
4 The adjusted p-value was obtained for the endpoints included in the hierarchical testing and was derived based on all the p-values from endpoints in order of the hierarchy up to the current endpoint. Unadjusted p-value was tested at the 5% significance level.

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 after 12 months of treatment (mean difference 1.55 points; p=0.0156). 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 stabilisation 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 treated with Evrysdi compared to placebo control (1.54 points [95% CI: 0.06, 3.02]; 1.49 points [95% CI: -0.94, 3.93], respectively).

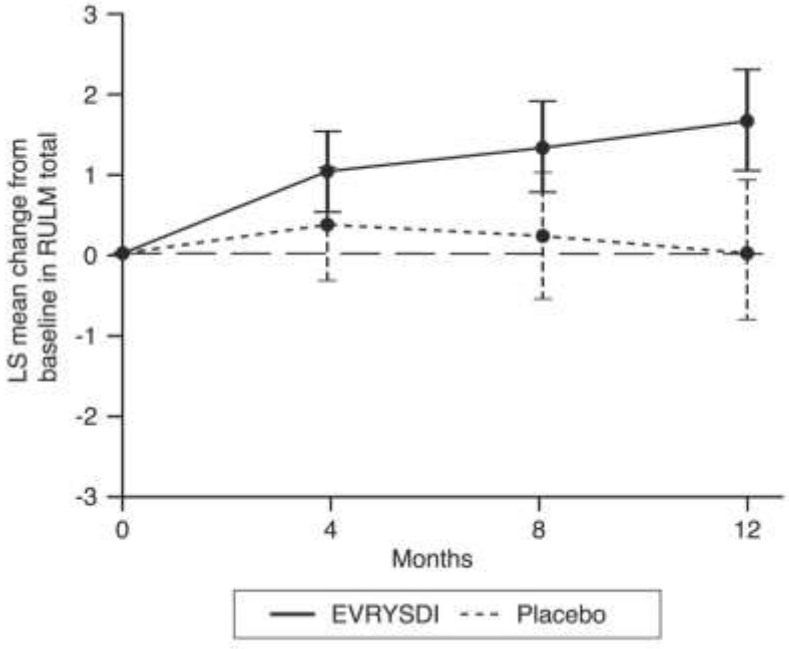
The study also met a secondary independent motor function outcome, RULM. On the RULM, statistically significant and clinically meaningful improvements in motor function were observed after 12 months of treatment compared to baseline. The patients 2-5 years old treated with Evrysdi demonstrated the greatest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

**Figure 3 Mean change from baseline in total MFM32 score over 12 months in SUNFISH Part 2[1]**




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

**Figure 4 Mean change from baseline in total RULM score over 12 months in SUNFISH Part 2[1]**




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

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

*SUNFISH Part 1*

The efficacy of Evrysdi in later-onset SMA patients was also supported by results from Part 1, the dose-finding part of SUNFISH. In Part 1, 51 patients with Type 2 and 3 SMA (including 7 ambulatory patients) between 2 to 25 years old were enrolled. After 1 year of treatment at the therapeutic dose (the dose selected for Part 2), there was a clinically meaningful improvement in motor function as measured by MFM32 with a mean change from baseline of 2.7 points (95% CI: 1.5, 3.8). The improvement in MFM32 was maintained up to 2 years on Evrysdi treatment (mean change of 2.7 points [95% CI: 1.2, 4.2]).

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

Use in Patients Previously Treated for SMA

Study BP39054 (JEWELFISH) is a single arm, open-label study to investigate the safety, tolerability, PK and PD of Evrysdi in patients with infantile-onset and later-onset SMA between 6 months and 60 years of age, who previously received treatment with SMA therapies (including nusinersen and onasemnogene abeparvovec). Of the 174 patients enrolled, 76 patients were previously treated with nusinersen (9 patients with Type 1 SMA, 43 with Type 2 SMA and 24 with Type 3 SMA) and 14 patients were previously treated with onasemnogene abeparvovec (4 patients with Type 1 SMA and 10 with Type 2 SMA). Patients had on average a greater than 2-fold increase in SMN protein levels in blood compared to baseline after 4 weeks of Evrysdi treatment.

## 5.2 PHARMACOKINETIC PROPERTIES

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

After administration of Evrysdi as an oral solution, the 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/mL. The estimated exposure for later-onset SMA patients (2-25 years old at enrolment) 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/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.

**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.

**Distribution**

The population PK 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 metabolised primarily by flavin monooxygenase 1 and 3 (FMO1 and FMO3), and also by CYPs 1A1, 2J2, 3A4 and 3A7.

Co-administration of 200 mg itraconazole twice daily, a strong CYP3A inhibitor, with a single oral dose of Evrysdi 6 mg 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 faeces 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**

Hepatic impairment

Mild and moderate hepatic impairment had no impact on the PK of Evrysdi. After administration of Evrysdi 5 mg, 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.

Renal impairment

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

Elderly

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.

Paediatrics

Body weight and age were identified as covariates in the population PK analysis. The dose is therefore adjusted based on age (below and above 2 years) and body weight (up to 20 kg) to obtain similar exposure across the age and body weight range. No data are available in patients less than 2 months of age.

Ethnicity

The PK of Evrysdi do not differ in Japanese and Caucasian subjects.

## 5.3 PRECLINICAL SAFETY DATA

### Genotoxicity

Risdiplam is not mutagenic in a bacterial reverse mutation assay. In mammalian cells *in vitro* and in the 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. These effects also manifest in other tissues with high cell turnover with changes in 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.

### Carcinogenicity

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

### 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, are stage-specific and reversible. No effects were seen on female reproductive organs in rats and monkeys after treatment with risdiplam.

**Reproductive toxicity**

In studies in pregnant rats treated with risdiplam, embryo-fetal toxicity with lower fetal weight and delayed development were evident. The no-observed-adverse-effect-level (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 (behavioural 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 rats showed that risdiplam crosses the placenta barrier and is excreted into milk.

**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, gastrointestinal tract, bone marrow), animal studies do not indicate any differences in sensitivity between juvenile, adolescent and adult animals.

**Other**

<u>Effect on retinal structure</u>

Chronic treatment of monkeys with risdiplam yielded evidence for an effect on the retina in terms of photoreceptor degeneration starting in the periphery of the retina. Upon cessation of treatment, the effects on the retinogram were partially reversible but the photoreceptor degeneration did not reverse. The effects were monitored by optical coherence tomography (OCT) and in the electroretinography (ERG). Some experimental data indicate that the effect may be caused by an impairment of photoreceptor recycling in the retinal pigment epithelium. The effect has a clear NOAEL at the clinical dose used for risdiplam. Effects were seen with exposures in excess of 2-times the exposure in humans at the therapeutic dose. No such findings were observed in albino or pigmented rats when dosed chronically with risdiplam at exposures exceeding those in the monkey. Such findings have not been observed in clinical trials in SMA patients with regular ophthalmological monitoring (including SD OCT and visual function assessment).

Effect on epithelial tissues

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

Effect on 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 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 haematological effects were seen with chronic treatment of rats over 26 weeks at the same exposure. The NOAEL for haematological 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. Haematological parameters remained unchanged during treatment with Evrysdi in clinical trials in SMA patients.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS

Mannitol
Isomalt
Strawberry flavour PHS-180152
Tartaric acid
Sodium benzoate
Macrogol 6000
Sucralose
Ascorbic acid
Disodium edetate

### 6.2 INCOMPATIBILITIES

No incompatibilities between Evrysdi and the oral syringes provided have been observed.

### 6.3 SHELF LIFE

The shelf life of the powder for oral solution is 24 months.

After reconstitution, 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.

## 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store powder in the original amber bottle below 25°C.

For storage conditions after reconstitution of the medicine, see section 6.3.

## 6.5 NATURE AND CONTENTS OF CONTAINER AND SPECIAL EQUIPMENT FOR USE

Evrysdi 750 microgram/mL powder for oral solution is supplied as powder in an amber glass bottle.

Each amber glass bottle contains 60 mg risdiplam in 2.0 g powder for oral solution. When reconstituted, the volume of the oral solution is 80 mL. Each mL of the reconstituted oral solution contains 750 micrograms of risdiplam.

Each carton contains: 1 bottle of risdiplam, 1 press-in bottle adapter, two 6 mL re-usable oral syringes and two 12 mL re-usable oral syringes.

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

The release of pharmaceuticals in the environment must be minimised. Medicines must not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

**Preparation of the powder for oral solution by a healthcare professional**

Evrysdi oral solution must be reconstituted by a healthcare professional prior to being dispensed. The reconstituted solution appears greenish yellow to yellow in colour.

Caution should be exercised during handling. Avoid inhalation and avoid direct contact with skin or mucous membranes with the dry powder and the reconstituted solution.

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

Instructions for reconstitution:

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 sterile water for injections into the bottle to yield the 750 microgram/mL oral solution.
4. Hold the medicine bottle on the table with one hand. Insert the press-in bottle adapter into the opening by pushing it down with the other hand. Ensure the adapter 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. If not, shake well again for after 15 seconds.
6. Write the "Discard after" date of the solution on the bottle label. (The "Discard after" date is calculated as 64 days after reconstitution, the day of reconstitution is counted as day 0). Put the bottle back in its original carton with syringes (in pouches) and "Instructions for Use – Administration" booklet.

Refer to the "Instructions for Reconstitution" provided in the pack.

## 7. MEDICINE SCHEDULE

Prescription Only Medicine

## 8. SPONSOR

Roche Products (New Zealand) Limited
PO Box 109113 Newmarket
Auckland 1149
NEW ZEALAND

Medical enquiries: 0800 276 243

## 9. DATE OF FIRST APPROVAL

27 January 2022

## 10. DATE OF REVISION

23 August 2022

**Summary table of changes**

| Section Changed | Summary of new information |
|---|---|
| 6.3 | Additional information for storage of oral solution is being provided based on new stability data. |