▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION
Evrysdi® (risdiplam)
Powder for oral solution and film-coated tablet

1. NAME OF THE MEDICINE

Risdiplam.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Evrysdi powder for oral solution
Evrysdi is available as a powder for oral solution. Each bottle is filled with 2.0 g of powder containing 60 mg of risdiplam. The powder is reconstituted to form an oral solution containing risdiplam 0.75 mg/mL

Evrysdi powder for oral solution contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

Excipients with known effect: contains benzoate and sucralose.

For the full list of excipients, see section 6.1.

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

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

Excipients with known effect: contains sugar alcohol.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Evrysdi powder for oral solution:
Evrysdi powder for oral solution 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 0.75 mg/mL of risdiplam (see section 4.2 Preparation of the powder for oral solution). The reconstituted solution is clear, greenish yellow to yellow in colour.

Evrysdi film-coated tablet:
Evrysdi tablets are pale yellow film-coated tablet, round and curved, with EVR debossed on one side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Evrysdi is indicated for the treatment of 5q spinal muscular atrophy (SMA).

4.2 DOSE AND METHOD OF ADMINISTRATION

SMA treatment should be initiated as early as possible after diagnosis.
Treatment with Evrysdi should be initiated and monitored by a specialist medical practitioner experienced in the diagnosis and management of SMA.

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

Evrysdi powder for oral solution
Evrysdi powder for oral solution, taken orally or enterally once reconstituted, is available for all age groups.

In infants who are breastfed, Evrysdi for oral solution can be administered before or after breastfeeding. Evrysdi cannot be mixed with formula or milk.

Evrysdi film-coated tablet
The Evrysdi film-coated tablet, taken orally or enterally, is available for patients prescribed the 5 mg dose.

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[a] and Body Weight	Recommended Daily Dose	Recommended Dosage Form
< 2 months of age	0.15 mg/kg	Powder for oral solution
2 months to less than 2 years of age	0.20 mg/kg	
2 years of age and older weighing less than 20 kg	0.25 mg/kg	
2 years of age and older weighing 20 kg or more	5 mg	Powder for oral solution or Film-coated tablet

[a] based on corrected age for preterm infants

The physician should prescribe the appropriate pharmaceutical form according to the dose required, and the patient's needs. For patients with difficulty swallowing a whole tablet, the tablet can be dispersed in non-chlorinated drinking water (e.g bottled water) or the powder for oral solution can be prescribed.

Dose changes must be made under the supervision of a healthcare professional (HCP).
Treatment with a daily dose above 5 mg has not been studied.

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.

Evrysdi powder for oral solution

Preparation of the powder for oral solution by a healthcare professional

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

Evrysdi powder for oral solution must be reconstituted by a HCP prior to being dispensed.

Caution should be exercised during handling. Avoid inhalation and avoid direct contact with skin or mucous membranes with the dry powder and/or 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 0.75 mg/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.

Method of administration

Evrysdi powder for oral solution
Refer to the "Instructions for Use – Administration" and the "Instructions for Reconstitution" provided in the pack.

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
1 mL	0.3 mL to 1.0 mL	0.01 mL
6 mL	1.0 mL to 6.0 mL	0.1 mL
12 mL	6.2 mL to 6.6 mL	0.2 mL

Select the correct oral syringes (1 mL, 6 mL or 12 mL) based on the patient's dosage and remove the other oral syringes from the carton/dispensing pack.

Use the re-usable oral syringe provided to deliver the daily dose of Evrysdi powder for oral solution. Patients should take Evrysdi powder for oral solution 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 some water after taking the reconstituted Evrysdi powder for oral solution to ensure the drug has been completely swallowed. If the patient is unable to swallow and has a nasogastric or gastrostomy tube, administer Evrysdi powder for oral solution via the tube. The tube should be flushed with water after delivering Evrysdi powder for oral solution.

Evrysdi film-coated tablet

Refer to the "Instructions for Use" provided in the pack for the preparation of the dispersion of Evrysdi film-coated tablet.

It is recommended that an HCP discuss with the patient or caregiver how to prepare the prescribed daily dose prior to administration of the first dose.

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

Swirl the cup gently for up to 3 minutes until fully mixed (though some particles will remain). If Evrysdi film-coated tablet is dispersed in non-chlorinated drinking water (e.g bottled water), take it immediately. To ensure no particles are left in the small cup, refill with at least one tablespoon (15mL) of non-chlorinated drinking water (e.g bottled water), swirl and administer immediately again.

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

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

If the patient is unable to swallow and has a nasogastric or gastrostomy tube, administer the dispersed Evrysdi film-coated tablet via a tube that is 8 French or higher. The tube should be flushed with the non-chlorinated drinking water (at least 15 mL) used to rinse the dispersion cup.

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

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 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 Clinical trials, 5.1 Clinical trials and 5.3 Preclinical safety data; Juvenile animal studies). No data on risdiplam pharmacokinetics are available in patients less than 16 days of age. The safety and efficacy of Evrysdi in preterm infants before reaching the corrected age of 16 days have not been established.

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 4.6 Use in pregnancy). 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).

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 Preclinical safety data, Retinal toxicity).

Type 0 or IV SMA

Patients most likely to develop type 0 or IV SMA have not been included in the clinical development program for Evrysdi. The decision to treat should be based on individualised expert evaluation of the expected benefits of treatment for that individual, balanced against the potential risk of treatment with Evrysdi. The full benefits and risks are unknown among patients diagnosed with type 0 or IV SMA.

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

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

Evrysdi has not been studied in paediatric patients below the age of 16 days. The safety and efficacy of Evrysdi in preterm infants before reaching the corrected age of 16 days have not been established (see section 5.1 Clinical trials and 5.3 Preclinical safety data; Juvenile animal studies).

Effects on laboratory tests

No data available.

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.

The potential of co-administered FMO1/3 inducers or inhibitors to affect risdiplam or M1 metabolite exposure was not investigated.

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 (11% increase in AUC; 16% increase in C_{max}). The extent of the interaction is not considered clinically relevant and therefore no dose adjustment is required for CYP3A substrates. Based on physiologically based pharmacokinetic (PBPK) modelling, a similar magnitude of the effect is expected in children and infants as young as 2 months old.
In vitro studies have shown that risdiplam and its major metabolite are not significant inhibitors of human MDR1, organic anion-transporting polypeptide (OATP)1B1, OATP1B3, organic anion transporter 1 and 3 (OAT 1 and 3) or organic cation transporter 2 (OCT2). Risdiplam and its metabolite are, however, *in vitro* inhibitors of the multidrug and toxin extrusion (MATE)1 and MATE2-K transporters. The effect of coadministration of risdiplam on the pharmacokinetics of MATE1 and MATE2-K substrates in humans is unknown. Based on in vitro data, Evrysdi may increase plasma concentrations of drugs eliminated via MATE1 or MATE2-K, such as metformin and fexofenadine. If co-administration cannot be avoided, monitor for drug-related toxicities and consider dosage reduction of the co-administered drug (based on the labelling of that drug) if needed.

Concomitant administration with other SMA therapies

There is no efficacy or safety data to support the concomitant use of risdiplam and nusinersen. Efficacy data for Evrysdi treatment when used in patients that previously received SMN1 gene therapy is not available.

Concomitant use with retinotoxic drugs

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

Effects on fertility

Male patients

Based on nonclinical findings, male fertility may be compromised while on treatment with Evrysdi. Based on observations from animal studies, the effects on sperm cells are expected to be reversible upon discontinuation of risdiplam.

Oral administration of risdiplam to rats for 4 (0, 1, 3, or 9 mg/kg/day) or 26 (0, 1, 3, or 7.5 mg/kg/day) weeks resulted in histopathological effects in the testis (degenerated spermatocytes, degeneration/atrophy of the seminiferous tubules) and epididymis (degeneration/necrosis of ductular epithelium) at the mid and/or high doses. At the high dose in the 26-week study, the testicular lesions persisted to the end of the recovery period, which corresponds, in rat, to approximately one spermatogenic cycle. The no-effect dose for adverse reproductive system effects in adult male rats (1 mg/kg/day) was associated with plasma drug exposures (unbound AUC) similar to that in humans at the Maximum Recommended Human Dose (MRHD) of 5 mg/day.

Adverse effects of risdiplam on the testis could not be fully evaluated in the monkey because the majority of monkeys tested were sexually immature. However, oral administration of risdiplam (0, 2, 4, or 6 mg/kg/day) for 2 weeks resulted in histopathological changes in the testis (increases in multinucleate cells, germ cell degeneration) at the highest dose. At the no-effect dose for testicular toxicity in monkeys, plasma exposures were approximately 1.6 times (unbound AUC) that in humans at the MRHD. Oral administration of risdiplam to post-weaning juvenile rats resulted in male reproductive toxicity (degeneration/necrosis of the testis seminiferous epithelium with associated oligo/aspermia in the epididymis and abnormal sperm parameters). The no-effect dose for adverse reproductive effects in post-weaning male juvenile rats was associated with plasma exposures approximately 2.4 times (unbound AUC) that in humans at the MRHD.

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. No effects were seen on female reproductive organs in rats and monkeys after treatment with risdiplam.

Patients of reproductive potential

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 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.

Use in pregnancy - Category D

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.

Oral administration of risdiplam (0, 1, 3, or 7.5 mg/kg) to pregnant rats throughout organogenesis resulted in decreased fetal body weights and increased incidences of fetal structural variations at the highest dose tested, which was not associated with maternal toxicity. The no-effect level for adverse effects on embryofetal development (3 mg/kg/day) was associated with maternal plasma exposure (unbound AUC) approximately 3 times that in humans at the maximum recommended human dose (MRHD) of 5 mg.

Oral administration of risdiplam (0, 1, 4, or 12 mg/kg) to pregnant rabbits throughout organogenesis resulted in embryofetal mortality, fetal malformations (hydrocephaly), and structural variations at the highest dose tested, which was associated with maternal toxicity. The no-effect dose for adverse effects on embryofetal development (4 mg/kg/day) was associated with maternal plasma exposure (unbound AUC) approximately 3 times that in humans at the MRHD.

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.

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.

Use in lactation

It is not known whether Evrysdi is excreted in human breast milk. Studies in rats show that risdiplam is excreted into milk. 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trials

The safety profile of Evrysdi is based on four clinical trials FIREFISH, SUNFISH, RAINBOWFISH 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 60.0 months (range: 0.6 to 61.7 months). The adverse events 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).

The safety profile for later-onset SMA patients between 2-25 years of age is based on the SUNFISH Part 2 study (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). 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, are provided in Table 4.

Tables 3 summarises the adverse events that have been reported with the use of Evrysdi in FIREFISH Part 1 and 2 during the 5-year extension period of study with an incidence ≥ 5% and SUNFISH Part 2 during the first 12 months of the placebo-controlled period, regardless of causality. Table 5 summarises the adverse events reported in SUNFISH Part 2 during the 5-year extension period of study with an incidence ≥ 5%, regardless of causality.

The corresponding frequency category for each adverse events 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 events from clinical trials are listed by MedDRA system organ class.

Table 3 Summary of adverse events reported in ≥ 5% of patients treated with Evrysdi for infantile-onset SMA observed in the FIREFISH study (Parts 1 and 2) during the 5 years of study period. A causal association has not been necessarily established

System Organ Class Adverse Events	Incidence N=62 n (%)	Frequency Category
Respiratory, thoracic and mediastinal disorders:		
Cough	8 (12.9)	Common
Respiratory Failure	4 (6.5)	Very common
Rhinorrhoea	6 (9.7)	Common
Respiratory distress	5 (8.1)	Common
Acute respiratory failure	4 (6.5)	Common
Atelectasis	4 (6.5)	Common
Nasal congestion	4 (6.5)	Common
General disorders and administration site conditions		
Pyrexia	40 (64.5)	Very common
Gastrointestinal disorders		
Constipation	16 (25.8)	Very common
Diarrhoea	16(25.8)	Very common
Vomiting	13 (21.0)	Very common
Teething	8 (12.9)	Very Common
Gastrooesophageal reflux disease	6 (9.7)	Common
Skin and Subcutaneous Tissue Disorders		
Rash[3]	20 (32.3)	Very common
Eczema	5 (8.1)	Common
Infections and infestations		
Ear infection	6 (9.7)	Common
Urinary Tract Infection	12 (19.4)	Common
Upper respiratory tract infection[1]	56 (90.3)	Very common
Lower respiratory tract infection[2]	42 (67.7)	Very common
Gastroenteritis	4 (6.5)	Common
Congenital, familial and genetic disorders		
Cryptorchidism	5 (8.1)	Common
Injury, poisoning and procedural complications		
Joint dislocation	5 (8.1)	Common
Metabolism and nutrition disorders		
Dehydration	4 (6.5)	Common
Musculoskeletal and connective tissue disorders		
Scoliosis	4 (6.5)	Common

System Organ Class Adverse Events	Incidence N=62 n (%)	Frequency Category
Renal and urinary disorders		
Haematuria	4 (6.5)	Common

[1] Includes upper respiratory tract infection, nasopharyngitis, COVID-19, rhinitis, influenza, respiratory tract infection, pharyngitis, respiratory tract infection viral, upper respiratory tract infection viral, laryngitis, sinusitis, upper respiratory tract infection bacterial

[2] Includes pneumonia (viral, bacterial and staphylococcal), COVID-19 pneumonia, lower respiratory tract infection, lower respiratory tract infection viral, tracheitis, bronchitis, bronchiolitis, tracheobronchitis, respiratory syncytial virus bronchiolitis

[3] Includes rash, rash maculo-papular, dermatitis allergic, erythema, dermatitis, rash papular, dermatitis acneiform, dermatitis atopic, rash erythematous, folliculitis

[4] Includes urinary tract infection, escherichia urinary tract infection, urethritis

Table 4 Summary of adverse events reported in ≥ 5% of patients treated with Evrysdi and with an incidence greater than on placebo observed in SUNFISH study (Part 2) – one year analysis

System Organ Class Adverse Events	Evrysdi N=120 n (%)	Placebo N=60 n (%)	Frequency Category
General disorders and administration site conditions			
Fever[1]	26 (22)	10 (17)	Very common
Gastrointestinal disorders			
Diarrhoea	20 (17)	5 (8)	Very common
Nausea	11 (9)	3 (5)	Common
Constipation	10 (8)	3 (5)	Common
Abdominal pain upper	7 (6)	2 (3)	Common
Skin and Subcutaneous Tissue Disorders			
Rash[2]	20 (17)	1 (2)	Very common
Mouth and aphthous ulcers	8 (7)	0 (0)	Common
Musculoskeletal and connective tissue disorders			
Arthralgia	6 (5)	0 (0)	Common
Infections and infestations			
Pneumonia	10 (8)	4 (7)	Common
Urinary tract infection[3]	6 (5)	0 (0)	Common
Nervous system disorders			
Headache	24 (20)	10 (17)	Very common

[1] Includes pyrexia and hyperpyrexia.

[2] Includes rash, erythema, rash maculo-papular, rash erythematous, rash papular, dermatitis allergic, and folliculitis.

[3] Includes urinary tract infection and cystitis.

Table 5 Summary of adverse events reported in ≥ 5% of patients treated with Evrysdi observed in SUNFISH study (Part 2) during the 5 years of study period. A causal association has not been necessarily established.

System Organ Class Adverse Events	**Evrysdi** N=179 n (%)	**Frequency Category**
Respiratory, thoracic and mediastinal disorders		
URTI[1]	151 (84.4)	Very common
Cough	36 (20.1)	Very common
Pneumonia	29 (16.2)	Very common
Bronchitis	23 (12.8)	Very common
Rhinorrhoea	15 (8.4)	Common
General disorders and administration site conditions		
Fever[2]	63 (35.2)	Very common
Influenza like illness	9 (5.0)	Common
Infections and infestations		
Influenza	20 (11.2)	Very common
Urinary tract infection[4]	23 (12.8)	Very common
Gastrointestinal disorders		
Vomiting	46 (25.7)	Very common
Diarrhoea	45 (25.1)	Very common
Gastroenteritis	29 (16.2)	Very common
Abdominal pain	20 (11.2)	Very common
Constipation	20 (11.2)	Very common
Nausea	19 (10.6)	Very common
Oropharyngeal pain	19 (10.6)	Very common
Abdominal pain upper	17 (9.5)	Common
Skin and Subcutaneous Tissue Disorders		
Rash[3]	35 (19.6)	Very common
Eczema	14 (7.8)	Common
Acne	9 (5.0)	Common
Musculoskeletal and connective tissue disorders		
Arthralgia	19 (10.6)	Very common
Pain in extremity	19 (10.6)	Very common
Back pain	17 (9.5)	Common
Nervous system disorders		
Headache	47 (26.3)	Very common
Renal and urinary disorders		
Haematuria	18 (10.1)	Very common
Psychiatric disorders		
Anxiety	10 (5.6)	Common
Ear and labyrinth disorders		
Ear pain	9 (5.0)	Common

[1] Includes upper respiratory tract infection, nasopharyngitis, COVID-19, pharyngitis, influenza, respiratory tract infection, rhinitis, sinusitis, viral upper respiratory tract infection, tonsillitis, laryngitis, respiratory syncytial virus infection, respiratory tract infection bacterial, respiratory tract infection viral, upper respiratory tract infection bacterial, viral pharyngitis, acute sinusitis, chronic sinusitis, coronavirus infection croup infectious, tonsillitis bacterial, viral rhinitis

[2] Includes pyrexia, hyperpyrexia, hyperthermia, febrile infection, body temperature increased, febrile convulsion.

[3] Includes rash, erythema, dermatitis, rash maculo-papular, rash erythematous, rash papular, dermatitis allergic, dermatitis atopic, dermatitis acneiform and folliculitis.

[4] Includes urinary tract infection, cystitis, pyelonephritis and urinary tract candidiasis

The RAINBOWFISH study is an open-label, single-arm study that enrolled 26 patients with pre-symptomatic SMA between 16 and 41 days of age at first dose. At the primary analysis, the median exposure duration was 20.4 months (range: 10.6 to 41.9 months) (see section 5.1 Clinical trials).

The safety profile of Evrysdi in pre-symptomatic patients in the RAINBOWFISH study is consistent with the safety profile for symptomatic SMA patients treated with Evrysdi in clinical trials.

Safety profile in patients treated previously with other SMA modifying therapies

Based on the analysis of the JEWELFISH study, the safety profile of Evrysdi in the treatment of non-naive SMA patients who received Evrysdi for a median of 59.6 months (including those previously on treatment with nusinersen (n=76) or with onasemnogene abeparvovec (n=14)) is consistent with the safety profile for treatment naive SMA patients treated with Evrysdi in the FIREFISH, SUNFISH and RAINBOWFISH clinical studies.

Post-marketing experience

The following adverse drug reactions have been identified from post-marketing experience with Evrysdi (Table 6). Adverse drug reactions are listed according to system organ classes in MedDRA.

Table 6 Adverse drug reactions from post-marketing experience

System Organ Class	Adverse Reaction	Frequency Category
Skin and Subcutaneous Tissue Disorders	Cutaneous vasculitis[1]	Unknown
Cardiac Disorders	Tachycardia[2]	Uncommon

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

[2] The frequency category for ADRs observed only in the postmarketing setting is defined as the upper limit of the 95% confidence interval calculated on the basis of the total number of patients exposed to Evrysdi in pivotal trials.

Description of selected adverse drug reactions from postmarketing experience

Cutaneous vasculitis - Symptoms recovered after permanent discontinuation of Evrysdi.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

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 information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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.

In vitro and in vivo data indicate that risdiplam may cause alternative splicing of additional genes, including FOXM1 and MADD. FOXM1 and MADD are thought to be involved in cell cycle regulation and apoptosis, respectively, and have been identified as possible contributors to adverse effects seen in animals.

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 for infantile-onset SMA and later-onset SMA patients, 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 at least 24 months (see section 5.1 Clinical trials).

Cardiac Electrophysiology

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

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. The efficacy of Evrysdi for the treatment of pre-symptomatic SMA patients was evaluated in the RAINBOWFISH study. The overall findings of these studies support the efficacy of Evrysdi for SMA patients. Patients with a clinical diagnosis of Type 0 and 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 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 symptoms 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 7 and displayed in Figure 1 and Figure 2.

Table 7 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%)
Survival and Event-Free Survival	**N=62[a]**	
Event-free survival[c]	87.1% (78.1%, 92.6%)	83.8% (74.3%, 90.1%)

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.

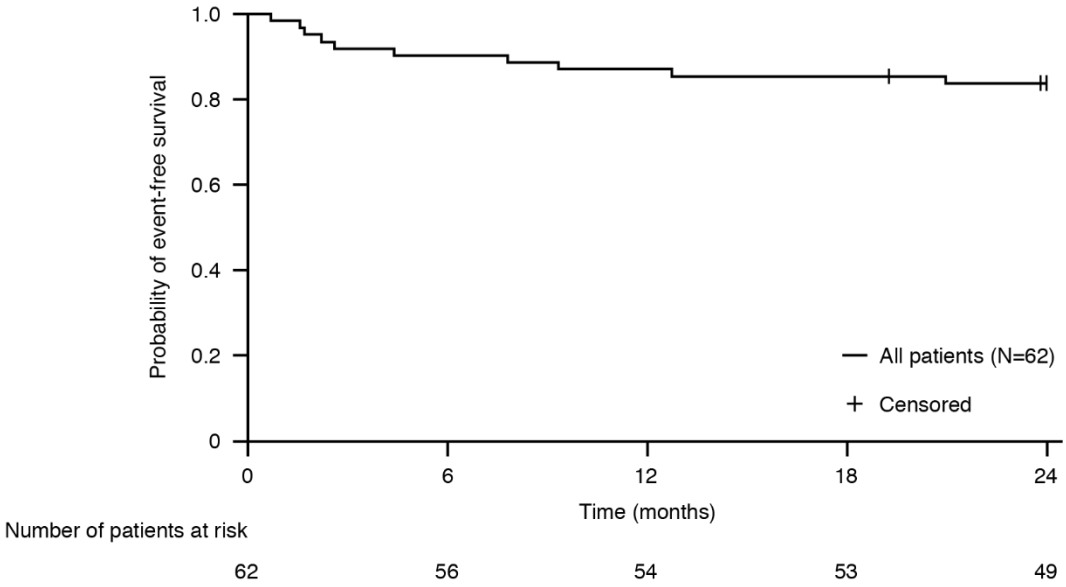
[c] An event is meeting the endpoint of permanent ventilation defined as tracheostomy or ≥16 hours of non-invasive ventilation per day or intubation for > 21 consecutive days in the absence of, or following the resolution of, an acute reversible event. Four patients met the endpoint of permanent ventilation 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. The improvements demonstrated at Month 24 were sustained until Month 60 with some patients showing further improvements. At Month 60, 80.5% of all patients were alive without permanent ventilation,

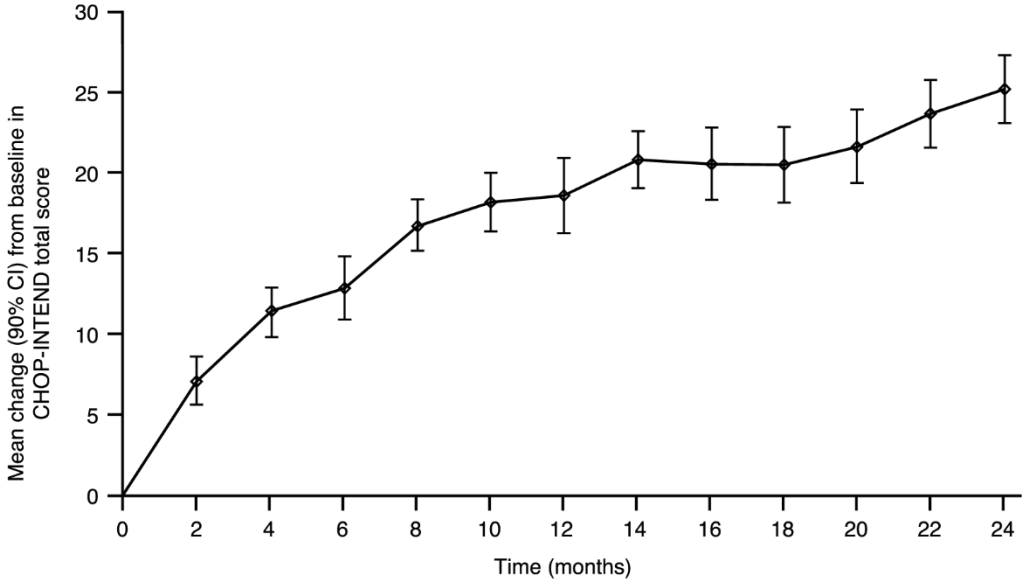
and 58.6% of patients who received the therapeutic dose could sit for 30 seconds (BSID-III, Item 26). In addition, 6.9% of patients could stand unaided and 10.3% could cruise (HINE-2), and 72.4% of patients were able to feed orally. These results indicate a clinically meaningful deviation from the natural history of untreated infantile-onset SMA. Untreated patients with infantile-onset SMA would never be able to sit without support and only 25% would be expected to survive without permanent ventilation beyond 14 months of age.

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



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

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



Later-onset SMA

Study BP39055 (SUNFISH), is a 2-part, 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 8 and Figures 3 and 4.

Table 8 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		

Endpoint	**Evrysdi** N=120	**Placebo** N=60
Proportion of patients with a change from baseline in MFM32 total score[1] of 3 or more at Month 12 (95% CI)	38.3% (28.9, 47.6)	23.7% (12.0, 35.4)
Odds ratio for overall response (95% CI) Adjusted p-value[3,4]	2.35 (1.01, 5.44) 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 p-value[2,4]	1.59 (0.55, 2.62) 0.0469	

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.

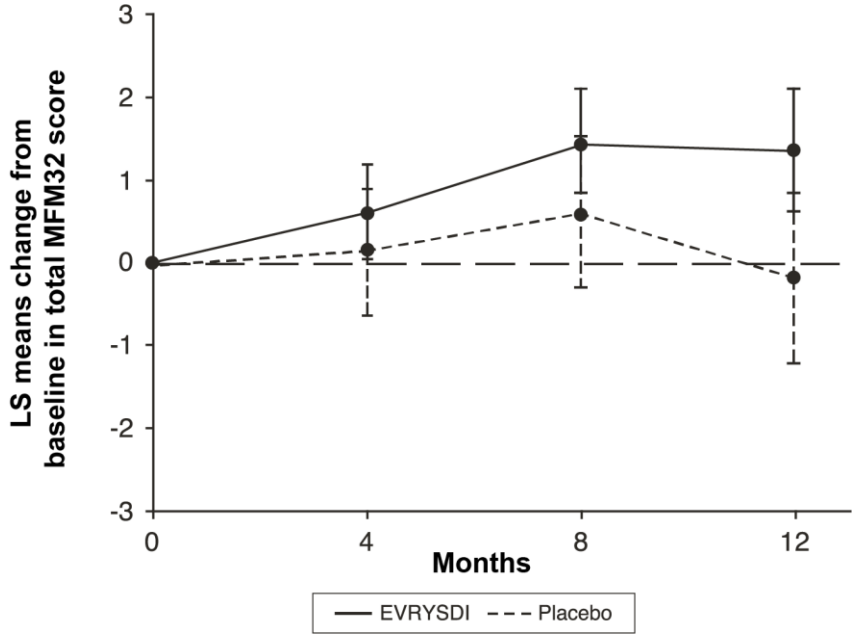
4 The adjusted p-value was obtained for the endpoints included in the hierarchical testing and was derived based on all the p-values from endpoints in order of the hierarchy up to the current endpoint.

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).

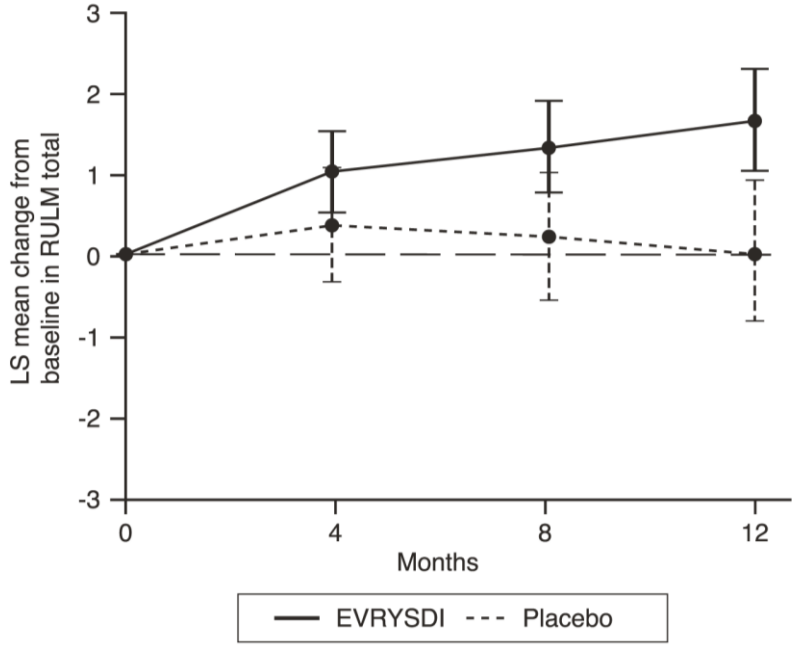
The study also met a secondary independent motor function outcome, RULM. On the RULM, statistically significant and clinically meaningful improvements in motor function were observed after 12 months of treatment compared to baseline. The patients 2-5 years old treated with Evrysdi demonstrated the greatest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

MFM32 was -0.08 (95% CI: -1.59, 1.43) and for RULM was 2.11 (95% CI: 1.01, 3.21) at month 60.

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]). At 5 years, the mean change from baseline in MFM32 was 1.38 (95% CI: -0.82, 3.58).

Pre-symptomatic SMA

Study BN40703 (RAINBOWFISH) is an open-label, single-arm, multicentre clinical study to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of Evrysdi in infants from birth to 6 weeks of age (at first dose) who have been genetically diagnosed with SMA but do not yet present with symptoms.

The efficacy in pre-symptomatic SMA patients was evaluated at Month 12 in 26 patients [intent-to-treat (ITT) population] who had been treated with Evrysdi. The median age of these patients at first dose was 25 days (range: 16 to 41 days), 62% were female and 85% were Caucasian. Eight patients, 13 patients and 5 patients had 2, 3 and ≥4 copies of the SMN2 gene, respectively. At baseline the median CHOP-INTEND score was 51.5 (range: 35 to 62), the median HINE-2 score was 2.5 (range: 0 to 6) 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 9 and 10, and Figure 5.

Table 9 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 10 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 Utilisation	
Proportion of patients with no hospitalisation[c]; (90 CI%)	92.3% (77.7%, 98.6%)
Event-free survival[d]	
Proportion of patients with Event-Free Survival;	100%

Efficacy Endpoints	ITT population (N=26)
(90 CI%)	(100%, 100%)

Abbreviations: CHOP-INTEND=Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI=Confidence Interval; ITT=Intent-to-treat

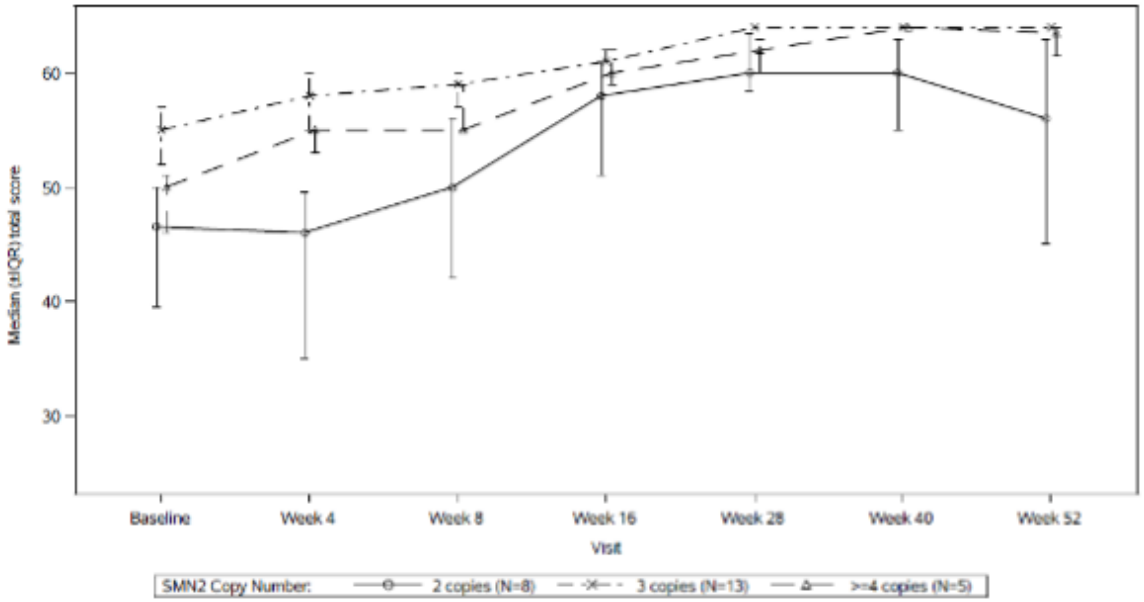
[a] Based on N=25.

[b] One patient was not assessed

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

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

Figure 5 Median Total CHOP-INTEND scores by visit and SMN2 copy number (ITT population)



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

Use in patients previously treated with other SMA modifying therapies

Study BP39054 (JEWELFISH, 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, 91.1% were non-ambulant, 83.3% of patients had scoliosis and 62.5% of patients had a Hammersmith Functional Motor Scale Expanded (HFMSE) score < 10 points.

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

Exploratory efficacy was assessed with age appropriate motor function measures including MFM-32 and RULM scales for patients 2-60 years of age, BSID-III and HINE-2 for patients

less than 2 years of age and the Six-Minute Walk Test (6MWT) in ambulant patients ≥ 6 years of age. At the analysis at month 24 of treatment, patients 2 - 60 years of age showed overall stabilisation 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.

Following 5 years of risdiplam treatment, patients 2-60 years of age showed a decline in motor function assessed by MFM-32, while the RULM was unchanged compared to baseline. All patients less than 2 years of age, assessed by the HINE-2 (n = 3), maintained or gained motor milestones such as head control, rolling, and sitting without support.. Of the 15 patients who were ambulant at baseline, 11 completed 5 years of treatment. Ten of these 11 patients (90.9%) retained their ability to walk.

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 pharmacokinetics of the Evrysdi tablet (swallowed or dispersed in water) demonstrated comparable bioavailability to the Evrysdi powder for oral solution in healthy adult subjects under fasted and fed conditions.

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 after 1 year of treatment and 2630 ng·h/mL after 5 years of treatment. For pre-symptomatic infants (16 days to ≤ 2 months) in the RAINBOWFISH study, the estimated exposure is 2020 ng·h/mL at 0.15 mg/kg after 2 weeks once daily administration. The estimated exposure for later-onset SMA patients (2-25 years old at enrolment) in SUNFISH study (Part 2) at the therapeutic dose (0.25 mg/kg once daily for patients with a body weight < 20 kg; 5 mg once daily for patients with a body weight ≥ 20 kg) was 2070 ng·h/mL after 1 year of treatment and 1940 ng·h/mL after 5 years of treatment. The estimated exposure (mean $AUC_{0\text{-}24h}$) for SMA treatment non-naïve patients (age 1-60 years at enrolment) was 1750 ng·h/mL at the therapeutic dose of 0.25 mg/kg or 5 mg. The observed maximum concentration (mean C_{max}) was 193 ng/mL in FIREFISH Part 2 and 140 ng/mL in SUNFISH Part 2, the estimated maximum concentration (mean C_{max}) at 0.15 mg/kg in RAINBOWFISH is 111 ng/mL, and 129 ng/mL in JEWELFISH study.

Absorption

Risdiplam exposure after administration of the film-coated tablet (swallowed or dispersed in water) was bioequivalent to the powder for oral solution. In the clinical studies, risdiplam was administered with a morning meal (high-fat, high calorie breakfast) or after breast feeding. Based on data in 47 healthy subjects, the T_{max} was delayed by up to 1 hour in fed state compared to that under fasted state.

Evrysdi powder for oral solution
Risdiplam was rapidly absorbed in the fasted state with a plasma t_{max} ranging from 1 to 5 hours after administration of powder for oral solution.

Evrysdi film-coated tablet

Risdiplam was rapidly absorbed in the fasted state with a plasma t_{max} ranging from 2 to 4.5 hours after oral administration of the film-coated tablet (swallowed or dispersed in water).

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%.

Metabolism

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}).

Excretion

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 months and 2 years) and body weight (up to 20 kg) to obtain similar exposure across the age and body weight range. No data are available in patients less than 16 days of age.

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Risdiplam was negative in a bacterial reverse mutation assay and in the Comet assay. In the mouse TK lymphoma cell assay *in vitro* and in the bone marrow of rats, risdiplam increased 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 similar to that 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.

Carcinogenicity

A 26 week carcinogenicity study with risdiplam (oral, up to 9 mg/kg/day) in rasH2 transgenic mice showed no tumourigenic potential in animals exposed up to 7-fold (based on total AUC) the exposure in humans at the therapeutic dose.
A 2-year carcinogenicity study in rats was conducted with daily oral doses of 0.3, 1, and 3 mg/kg of Evrysdi. Evrysdi did not induce tumours at the low and mid-dose, where observed exposures in rats were equivalent to those in humans at the maximum recommended human dose (MRHD) of 5 mg. Statistically significant increases in tumours of the preputial gland in male rats and clitoral gland in female rats were seen at the high dose with 6 times the exposure of the MRHD. As these are both rodent-specific organs, these findings have no human relevance.

Retinal toxicity

Risdiplam-induced functional and structural retinal abnormalities were seen in animal studies. In a 39-week toxicity study in monkeys, oral administration of risdiplam (0, 1.5, 3, or 7.5/5 mg/kg/day; high dose lowered after 4 weeks) produced functional abnormalities on the electroretinogram (ERG) in all mid-and high-dose animals at the earliest examination time (Week 20). These findings were associated with retinal degeneration, detected by optical coherence tomography (OCT), on Week 22, the first examination time. The retinal degeneration, with peripheral photoreceptor loss, was irreversible. A no-effect dose for the retinal findings (1.5 mg/kg/day) was associated with plasma exposures (AUC) similar to that in humans at the maximum recommended human dose (MRHD) of 5 mg.

Effect on epithelial tissues

Oral administration of risdiplam to rats and monkeys resulted in histopathological changes in epithelium of the gastrointestinal (GI) tract (apoptosis/single cell necrosis), lamina propria (vacuolation), the exocrine pancreas (single cell necrosis), the skin, tongue, and larynx (parakeratosis/hyperplasia/degeneration) with associated inflammation. The skin and GI epithelial effects were reversible. The no-effect doses for effects on epithelial tissues in rats and monkeys were associated with plasma exposures (AUC) similar to that in humans at the MRHD.

Juvenile animal studies

Oral administration of risdiplam (0, 0.75, 1.5, 2.5 mg/day) to young rats from postnatal day (PND) 4 through PND 31 resulted in decreased growth (body weight, tibia length) and delayed sexual maturation in males at the mid and high dose. The skeletal and body weight deficits persisted after cessation of dosing. Decreases in absolute B lymphocyte counts were seen at the high dose. Decreases in testis and epididymis weights, which correlated with degeneration of the seminiferous epithelium in the testis, occurred at the mid and high doses; the histopathology findings were reversible, but organ weight persisted after cessation of dosing. Impaired female reproductive performance (decreased mating index, fertility index, and conception rate) was observed at the high dose. At the NOAEL (1.5 mg/kg/day) the plasma exposure (unbound AUC) was 2.4 × that in humans at the maximum recommended human dose (MRHD) of 5 mg/day.

Oral administration of risdiplam (0, 1, 3, or 7.5 mg/day) to young rats from PND 22 through PND 112 produced a marked increase in micronuclei in the bone marrow, male reproductive organ histopathology (degeneration/necrosis of the seminiferous tubule epithelium, parameters (decreased sperm concentration and motility, increased sperm morphology abnormalities) at the highest dose tested. Increases in T lymphocytes (total, helper, and cytotoxic) were observed at the mid and high doses. The reproductive and immune effects persisted after cessation of dosing. At the NOAEL (3 mg/kg/day) plasma exposures (unbound AUC) were similar to that in humans at the MRHD.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Evrysdi powder for oral solution
Mannitol
Isomalt
Strawberry flavour PHS-180152 {PI# 131279}
Tartaric acid
Sodium benzoate
Macrogol 6000
Sucralose
Ascorbic acid
Disodium edetate

Evrysdi film-coated tablet

Tablet core
Tartaric acid
Mannitol
Microcrystalline cellulose
Colloidal anhydrous silica
Crospovidone
Sodium stearyl fumarate
Strawberry flavour PHS-180152 {PI# 131279}

Film-coat white (Opadry II complete film coating system 85F18422 white {PI#: 11376} or Opadry II complete film coated system 85F18422-CN white {PI# 144540})
Polyvinyl alcohol
Titanium dioxide
Macrogol 3350
Purified Talc

Film-coat yellow (Opadry II complete film coating system 85F220022 yellow {PI# 144602}) or Opadry II complete film coating system 85F220022 CN yellow {PI# 148812}),
Polyvinyl alcohol
Titanium dioxide
Macrogol 3350
Purified Talc
Iron oxide yellow

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Evrysdi powder for oral solution

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

- Evrysdi should not be used after the expiry date ("EXP" for the powder) on the carton and on the bottle.

Reconstituted oral solution

Store in a refrigerator at 2°C–8°C. 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 amber bottle and keep the bottle always in an upright position with the cap tightly closed.

After reconstitution, the oral solution should not be used and should be discarded:
- after 64 days (refer to “Discard After” date written on the bottle),
- if the oral solution is kept outside of the refrigerator for more than a total combined time of 5 days at room temperature (below 40˚C),
- or if the oral solution is kept above 40˚C.

Evrysdi film-coated tablet
Store below 30°C. Keep in the original package to protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

Evrysdi powder for oral solution
Evrysdi 0.75 mg/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 0.75 mg of risdiplam.

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

Evrysdi film-coated tablet
Evrysdi 5 mg film coated tablet is packaged in Al/Al blister.
Pack sizes: 28 tablets (4 x blister strips containing 7 tablet each inside carton).

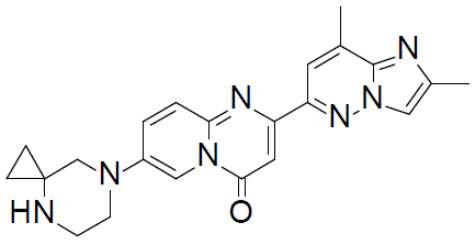
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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.

6.7 PHYSICOCHEMICAL PROPERTIES

Risdiplam has a molecular weight of 401.46 g/mol and a partition coefficient (log P) of 1.46. Risdiplam is a weakly basic compound exhibiting high aqueous solubility in low pH media (pH < 4) and poor solubility at pH 4 and above.

Chemical structure:



CAS-number: 1825352-65-5

Chemical name: 7-(4,7-diazaspiro[2.5]octan-7-yl)-2-(2,8dimethylimidazo[1,2-*b*]pyridazin-6-yl)pyrido-*4H*-[1,2-*a*]pyrimidin-4-one.

Empirical formula: $C_{22}H_{23}N_7O$.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8. SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
Level 8, 30-34 Hickson Road
Sydney NSW 2000
AUSTRALIA

Medical enquiries: 1800 233 950

9. DATE OF FIRST APPROVAL

02 June 2021

10. DATE OF REVISION

10 September 2026

Summary table of changes

Section Changed	Summary of new information
4.2	Addition of a new route of administration for Evrysdi tablets
4.8, 5.1, 5.2	Addition of 5-year JEWELFISH data