Date: 30 January 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Evrysdi

International non-proprietary name: risdiplam

Pharmaceutical form: powder for oral solution

Dosage strength(s): 0.75 mg/mL

Route(s) of administration: oral

Marketing Authorisation Holder: Roche Pharma (Schweiz) AG

Marketing Authorisation No.: 67251

Decision and Decision date: extension of therapeutic indication approved on 12 December 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BSID-III	Bayley Scales of Infant and Toddler Development – Third Edition
BW	Body weight
CMAP	Compound muscle action potential
CCOD	Clinical cut-off date
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDA	Food and Drug Administration (US)
GLP	Good Laboratory Practice
HINE-2	Hammersmith Infant Neurological Examination Module 2
HPLC	High performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International nonproprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetic
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SAE	Serious adverse event
SMA	Spinal muscular atrophy
SMN	Survivor motor neuron
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a[decies] no. 2 of the TPA.
The Orphan Status was granted on 15 October 2018.

Extension(s) of the therapeutic indication(s)
The applicant requested to add or change the indication in accordance with Article 23 TPO.

2.2 Indication and Dosage

2.2.1 Requested Indication

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

2.2.2 Approved Indication

Evrysdi is indicated for the treatment of 5q-associated spinal muscular atrophy (SMA) in paediatric and adult patients.

2.2.3 Requested Dosage

Summary of the applied standard dosage:
Evrysdi is taken orally once a day, at approximately the same time each day.
The recommended once-daily dose is determined by age and body weight (see Table):

Age and body weight	*Recommended daily dose*
16 days < 2 years	0.20 mg/kg
≥ 2 years (< 20 kg)	0.25 mg/kg
≥ 2 years (≥ 20 kg)	5 mg

Dosage 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 aged below 16 days.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	22 December 2021
Formal control completed	8 February 2022
List of Questions (LoQ)	8 June 2022
Answers to LoQ	6 July 2022
Predecision	28 September 2022
Answers to Predecision	23 October 2022
Final Decision	12 December 2022
Decision	approval

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3 Medical Context

Spinal muscular atrophy (SMA) is a group of inherited autosomal recessive neuromuscular disorders characterised by loss of nerve cells in the brainstem and the spinal cord (lower motor neurons), leading to muscle weakness and atrophy. SMA is associated with mutations in the survivor motor neuron (SMN) genes, resulting in SMN protein deficiency.

Types of SMA

SMA is divided into subtypes (SMA types 0 to IV) based on age of symptom onset and maximum motor function achieved, with a lower number representing a younger age of onset and more severe disease.

Type	Age of Onset	Maximal Motor Milestone	Motor Ability and Additional Features	Prognosis[c]
SMA 0	Before birth	None	Severe hypotonia; unable to sit or roll[a]	Respiratory insufficiency at birth; death within weeks
SMA I	2 weeks (Ia) 3 months (Ib) 6 months (Ic)	None	Severe hypotonia; unable to sit or roll[b]	Death/ventilation by 2 years
SMA II	6 to 18 months	Sitting	Proximal weakness; unable to walk independently	Survival into adulthood
SMA III	<3 years (IIIa) >3 years (IIIb) >12 years (IIIc)	Walking	May lose ability to walk	Normal life span
SMA IV	>30 years or 10 to 30 years	Normal	Mild motor Impairment	Normal life span

[a]Need for respiratory support at birth; contractures at birth, reduced fetal movements.
[b]Ia joint contractures present at birth; Ic may achieve head control.
[c]Prognosis varies with phenotype and supportive care interventions.

(Source: Farrar MA et al. Emerging Therapies and Challenges in Spinal Muscular Atrophy. Ann Neurol 2017; 81:355-368)

The incidence rates for SMA types I, II and III are estimated at 5.5, 1.9 and 1.7 per 100.000 live births, respectively[1].
Newborn screening facilitates early identification of infants with SMA.

Currently available treatment options

Currently available treatment options can be subdivided into SMN-dependent gene therapies, which act as a splicing modifier of SMN2 (nusinersen, risdiplam), SMN1-replacing gene therapies (onasemnogene abeparvovec) and treatments targeting SMN-independent factors (muscle-enhancing therapies and neuroprotection)[2].

Approved medicinal products for SMA in Switzerland (December 2022)

Currently approved treatments for SMA in Switzerland are Spinraza® (nusinersen), Evrysdi® (risdiplam) and Zolgensma® (onasemnogene abeparvovec). For details see www.swissmedicinfo.ch.

[1] Ingrid, E.C.; Verhaart, I.E.C.; Robertson, A.; Wilson, I.J.; Aartsma-Rus, A.; Cameron, S.; Jones, C.C.; Cook, S.F.; Lochmüller, H. Prevalence, incidence and carrier frequency of 5q–linked spinal muscular atrophy–A literature review. Orphanet J. Rare Dis. 2017, 2, 124

[2] Messina S et al. New Treatments in Spinal Muscular Atrophy: Positive Results and New Challenges.J Clin Med. 2020, 9, 2222; doi:10.3390/jcm9072222

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4 Nonclinical Aspects

The applicant did not submit new nonclinical studies to support the requested indication extension. This was considered acceptable. The route of administration remains unchanged; the applicant relied on clinical data for the adapted posology.

Based on the ERA, the indication extension will not be associated with a significant risk for the environment.

From the nonclinical point of view, there are no objections to approval of the proposed indication extension.

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5 Clinical and Clinical Pharmacology Aspects

5.1 Dose Finding and Dose Recommendation

Based on pharmacokinetic (PK) data with a clinical cut-off date (CCOD) in August 2021, the dose of risdiplam selected to achieve the target exposure was 0.2 mg/kg. Therefore, a once-daily oral dose of 0.2 mg/kg risdiplam was selected as the pivotal dose for the Phase 2 Study BN40703 (RAINBOWFISH) in patients aged below 2 monthswith pre-symptomatic, genetically diagnosed spinal muscular atrophy (SMA). Further, it was first proposed by the Marketing Authorisation Holder (MAH) as the recommended dosing regimen for all infants aged between 16 days and 2 years.

Nevertheless, the dose recommendation in the youngest patient population aged < 2 months was assessed as not sufficient based on the interim data of the pivotal RAINBOWFISH study at the time of application.

The MAH provided an updated PK data analysis and simulations (CCOD in April 2022) with its responses to the List of Questions (LOQ).

Based on this updated analysis, the dosing regimen of 0.15 mg/kg was supported and is now proposed for infants aged between 16 days and < 2 months.

Children aged < 16 days were not studied and no dose recommendation can be made for this age group.

5.2 Clinical Pharmacology

Special Populations

The existing PopPK model (“reference model”) describing the risdiplam pharmacokinetics in SMA patients aged 0.18 to 61 years was employed to analyse additional (Month 24 visit) data from Study BP39056 (FIREFISH) and the PK data from Study BN40703 available up to 8 April 2022.

The risdiplam PopPK model was a three-transit compartment absorption model connected to a systemic linear two-compartment PK model. Inter-individual variability (IIV) was estimated for the absorption transit rate (ktr), the apparent clearance (CL/F) and the apparent central volume of distribution (Vc/F). Proportional residual errors were estimated separately for venous and capillary samples. Time-varying body weight (BW) (power model structure with estimated allometric exponents) was included as a covariate of the model on CL/F, apparent inter-compartmental clearance (Q/F), Vc/F and apparent peripheral volume of distribution (Vp/F). Time-varying age (maturation function with sigmoid model structure) was included as a covariate of the model on CL/F and Vc/F. A factor for CL/F of healthy adults was also included as a covariate.

The reference model with the unchanged parameter estimates from the prior analysis included in the primary submission described the Month 24 data of Study BP39056 quite well. The age of the patients in Month 24 was 2.18 – 2.69 years, i.e. within the range of the patient population used for the development of the model. As in the primary analysis, the goal of achieving an $AUC_{0\text{-}24h}$ of about 2000 ng*h/mL was met.

The situation was different for the patients from Study BN40703 (RAINBOWFISH). The age of these patients at the first risdiplam dose was 0.04 – 0.11 years (16 to 41 days), extending the overall age range of the analysis population to 0.04 – 61 years. The dataset also included the above-mentioned data from Study BP39056. Only one patient from Study BN40703 was actually 16 days old at the first risdiplam dose. All other patients were ≥ 20 days old.

Even after re-estimation of the PK parameters and adjustment of the reference body weight for allometric scaling, the reference model over-predicted the risdiplam plasma concentration in the BN40703 study population at the early measuring points.

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The reference model was adapted by the inclusion of an additional fraction of CL/F at birth in the maturation function of risdiplam CL/F. This modification resulted in a considerable improvement in the BN40703 data fit. The final model described the overall data well.

As data from only 26 patients from Study BN40703 were available, no formal covariate analysis was done. However, graphical evaluations did not indicate any covariate relationships other than age and body weight.

As in the prior analyses, the target was to achieve a risdiplam mean $AUC_{0\text{-}24h}$ of 2000 ng*h/mL in the paediatric patients. The estimated mean risdiplam $AUC_{0\text{-}24h}$ was close to 3000 ng*h/mL in children aged between 16 days and 2 months after administration of 0.2 mg/kg. In contrast, the proposed dose of 0.15 mg/kg resulted in mean $AUC_{0\text{-}24h}$ values of 2080 and 2200 ng*h/mL on Day 14 and 28, respectively.

The M1 metabolite/parent ratio of the BN40703 patients was comparable to the older SMA patients. Risdiplam plasma protein binding was also comparable. The free fraction was 13.1% in the BN40703 patients and 9.9% to 10.1% in the older SMA patients.

In summary, the dose of 0.15 mg/kg for children aged 16 days to < 2 months is reasonable from a pharmacokinetic point of view.

5.3 Efficacy

Study BN40703 (RAINBOWFISH)

Study BN40703 (RAINBOWFISH) is an open-label, single-arm, multicentre clinical study to investigate the efficacy, safety, pharmacokinetics and pharmacodynamics of risdiplam in infants aged from birth to 6 weeks (at first dose) who are genetically diagnosed with SMA (SMN1 deletion and any SMN2 copies) but not yet presenting with symptoms.

The study is still ongoing. Enrolment will continue until at least 25 patients are enrolled (including a minimum of 5 patients who meet the criteria for the primary efficacy population) or until a total of 10 patients who meet the criteria for the primary efficacy population are enrolled.

The current submission is based on data from an interim analysis (CCOD: 1 July 2021) with 18 young infants with pre-symptomatic SMA. These patients were mostly diagnosed by newborn screening or had a family history of SMA. The SMN2 copy number varied (N=7 with 2 copies, N=7 with 3 copies and N=4 with ≥ 4 copies).

The primary endpoint analysis of the study (infants sitting without support for 5 seconds after 12 months of treatment, as assessed by Item 22 of BSID-III) was not conducted at this time point to preserve Type I error. Per protocol, the primary efficacy analysis will be conducted when the last patient enrolled (irrespective of SMN2 copy number) has reached 12 months of treatment (expected in mid-2023).

The current interim efficacy data provided only preliminary data on secondary efficacy endpoints from 7 infants aged 16 to 40 days [mean age 35 days] at first dose (N=4 with 2 copies, N=2 with 3 copies and N=1 with ≥ 4 copies of SMN2) who completed at least 12 months of treatment.

Overall, important motor milestones and high levels of monitor function were achieved in these patients:

- All 7 patients were able to sit without support (HINE-2 categories of ‘Stable sit’ [N=1] and ‘Pivots (rotates)’ [N=6]).
- High levels of motor function illustrated by the median score on the Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) were achieved and maintained at Month 12 (maximum score in 5 infants). 2 patients with a baseline CMAP amplitude < 1.5 mV increased their motor function over time.

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For further details, please consult the “Properties/effects” and “Clinical efficacy” sections of the Information for healthcare professionals.

5.4 Safety

The safety data were derived from an interim analysis of 18 patients exposed to risdiplam regardless of treatment duration, with a CCOD of 1 July 2021.

The most frequent adverse events (AEs) (> 2 patients) by system organ class (SOC) were: gastrointestinal disorders, and infections and infestations (50.0% [9 patients] each); respiratory, thoracic and mediastinal disorders, and skin and subcutaneous tissue disorders (38.9% [7 patients] each); and general disorders and administration site conditions (27.8% [5 patients]).

The most frequent adverse events (AEs) (> 2 patients) by preferred term (PT) were: teething (33.3% [6 patients]); nasal congestion and pyrexia (27.8% [5 patients] each); diarrhoea, vomiting and viral infection (22.2% [4 patients] each); constipation, cough and eczema (16.7% [3 patients] each).

Upper respiratory tract infections (basket of terms) were reported in 3 patients (16.7%) who experienced a total of 7 AEs.

Lower respiratory tract infections (basket of terms) were reported in 1 patient (5.6%) who experienced 1 AE of bronchiolitis.

Updated safety data with a CCOD of 25 February 2022 were provided with the responses to the List of Questions.

This dataset included data from 26 enrolled patients on risdiplam treatment ranging from 0.3 months to 30.1 months and increased the number of pre-symptomatic patients treated with risdiplam for ≥ 12 months from 7 to 11 patients.

The available updated short-term safety data are in line with the known safety profile of Evrysdi. No new adverse drug reactions (ADRs) or prohibitive safety signals could be identified.

5.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Clinical Pharmacology

The dose of 0.15 mg/kg for children aged 16 days to < 2 months is reasonable from a pharmacokinetic point of view.

Clinical

Despite the limitations of the clinical data with regard to number of patients studied and duration of observation period, the benefit-risk ratio is considered to be positive for the submitted line extension of Evrysdi to pre-symptomatic neonates and infants with SMA below the age of 2 months.

The dose recommendation for the youngest patient population aged 16 days to < 2 months is 0.15 mg/kg.

No dose recommendation can be provided for patients aged below 16 days.

As a post-approval requirement the final clinical study report (CSR) of RAINBOWFISH has to be submitted in due course.

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6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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7 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Evrysdi was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new
safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Evrysdi®

Composition

Active substances

Risdiplam.

Excipients

Mannitolum, isomaltum (E953) 2.97 mg/1 ml, acidum tartaricum, natrii benzoas (E211) 0.38 mg/1 ml, macrogolum 6000, sucralosum, acidum ascorbicum, dintarii edetas, strawberry aroma, maltodextrinum et modified starch (E1450).

80 ml of prepared Evrysdi solution contains 7,2 mg sodium.
1 ml ready to use solution contains 0,09 mg sodium.

Pharmaceutical form and active substance quantity per unit

Evrysdi 0,75 mg/ml powder for oral solution is yellowish to greenish, yellow greyish. The powder is contained in a brown glass bottle. One bottle contains 60 mg risdiplam in 2 g powder. After preparation of the oral solution with purified water or water for injection, the final volume is 80 ml. 1 ml solution contains 0,75 mg risdiplam (see section "Other instructions", Instructions for handling).

Indications/Uses

Evrysdi is indicated for the treatment of 5q-associated spinal muscular atrophy (SMA) in paediatric and adult patients.

Dosage/Administration

Evrysdi oral solution must be prepared by a medical professional (e.g. physician or pharmacist) prior to being dispensed.

It must be ensured that a medical professional discusses with the patient or carer how the prescribed daily dose is to be prepared and taken, before the first dose is administered (see “Other Information” section, Information for handling).

Initiation and monitoring of treatment with Evrysdi must be undertaken by physicians experienced in diagnosing and treating patients with spinal muscular atrophy.

The clinical development programme did not include type IV SMA patients.

Usual dosage

Evrysdi is taken or given once a day, at approximately the same time each day, using the reusable syringes for oral administration provided in the pack.
The recommended once daily dose of Evrysdi for the treatment of SMA is determined by age and body weight of the patient (see Table 1).

Table 1: Dosing Regimen by Age and Body Weight

Age[a] and Body Weight	***Recommended Daily Dose***
16 days to <2 months	0,15 mg/kg
2 months to < 2 years of age	0.20 mg/kg
≥ 2 years of age (< 20 kg)	0.25 mg/kg
≥ 2 years of age (≥ 20 kg)	5 mg

[a] based on corrected age for preterm infants

Dose changes must be made under the supervision of a healthcare professional. Treatment with a daily dose above 5 mg has not been studied to date. No data are available in infants below 16 days of age.

Patients with impaired hepatic function

No dose adjustment is required in patients with mild or moderate hepatic impairment. Evrysdi has not been studied in patients with severe hepatic impairment (see section “Pharmacokinetics”, Kinetics in specific patient groups).

Patients with impaired renal function

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 “Pharmacokinetics”, Kinetics in specific patient groups).

Elderly patients

Clinical studies of Evrysdi did not include patients aged 65 years and over, therefore, it was not determined whether they respond differently to the medication than younger patients.

Children and adolescents

Limited data is available on the safety and efficacy of Evrysdi in paediatric patients under 2 months of age. No data is available for premature infants or newborns under 16 days of age (see section “Clinical Efficacy”).

Delayed administration

Evrysdi is taken orally once daily at approximately the same time each day. If a dose of Evrysdi is missed, it should be taken as soon as possible if still within 6 hours of the scheduled dose. Otherwise, skip the missed dose and take the normal dose at the regularly scheduled time the next day.
If a dose is not fully swallowed or vomiting occurs after taking 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.

Mode of administration

For the administration of the daily dose of Evrysdi, the reusable syringe for oral administration contained in the package should be used.

Selecting the appropriate reusable oral syringe for the prescribed daily dose

Table 2: Selecting the appropriate syringe for oral administration of the prescribed daily dose of Evrysdi

Syringe Size	Dosing Volume	Syringe Increments
1 ml	0,3 ml to 1,0 ml	0,01 ml
6 ml	1,0 ml to 6,0 ml	0,1 ml
12 ml	6,2 ml to 6,6 ml	0,2 ml

For the calculation of dosing volume, the volume increments of the oral syringe also need to be considered. The dose volume is rounded up or rounded down to the closest volume increment marked on the selected oral syringe (e.g. 6,3 ml to 6,4 ml, 3,03 ml to 3,0 ml and 1,05 to 1,1 ml).

The patient should take the Evrysdi solution immediately after it is drawn up into the reusable oral syringe. If the content of the syringe is not taken or administered within 5 minutes, the dose should be discarded (see section “Disposal of unused/expired medicines”) and a new dose should be prepared.

Evrysdi should be administered after a meal. The patient should drink some water after taking Evrysdi to ensure the medication has been completely swallowed. If the patient is unable to swallow and has a nasogastric or gastrostomy tube, administer Evrysdi via the tube. The tube should be flushed with water after delivering Evrysdi (see section ”Other Information”, Instructions for handling).

Contraindications

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

Warnings and precautions

General

In animal studies, retinal changes, epithelial changes, particularly of the skin and the gastrointestinal tract, and indications of bone marrow toxicity (changes to complete blood count) were observed. The risk that such changes may also occur in humans cannot be conclusively assessed at present due to limited long-term safety data.

Embryo-foetal Toxicity

Embryo-foetal toxicity has been observed in animal studies (see section “Preclinical data”). Patients of reproductive potential should be informed of the risks and must use highly effective contraception during treatment and for 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 “Dosage/Administration”).

Potential Effects on Male Fertility

Due to reversible effects of Evrysdi on male fertility based on observations from animal studies, male patients should not donate sperm while on treatment and for 4 months after the last dose of Evrysdi (see section “Pharmacokinetics”, Kinetics in specific patient groups and section Preclinical data).

Skin contact with the powder and reconstituted oral solution is to be avoided. However, if the medicinal product (powder or solution) gets on the skin, the area should be washed with water and soap.

This medicinal product contains 0,38 mg sodium benzoate per 1 ml. This medicine contains less than 1 mmol sodium (23 mg) per dose, i.e. it is nearly "sodium-free".

This medicinal product contains isomaltol. Patients with the rare hereditary fructose intolerance should not use this medicine.

Interactions

Effects of Evrysdi on other medicinal products

In vitro risdiplam and its major circulating metabolite M1 did not induce CYP1A2, 2B6, 2C8, 2C9, 2C19 or 3A4. *In vitro* risdiplam and M1 did not inhibit (reversible or time-dependent inhibition) any of the CYP enzymes tested (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6) with the exception of CYP3A. Risdiplam is a weak inhibitor of CYP3A. In healthy adult subjects, administration of Risdiplam once daily for 2 weeks slightly increased the exposure of midazolam, a highly sensitive CYP3A substrate (AUC 11%; Cmax 16%). The extent of this 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 this effect is expected in children and infants starting at 2 months of age.

In vitro studies have shown that risdiplam and its major metabolite are not significant inhibitors of human MDR1, organic anion-transporting polypeptides (OATP) 1B1, OATP1B3, as well as organic anion transporters 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 active substance concentrations, no interaction is expected with OCT2 substrates. The effect of co-administration of risdiplam on the pharmacokinetics of MATE1 and MATE2-K substrates in human is unknown. Based on *in vitro* data, Evrysdi may increase plasma concentrations of drugs eliminated via MATE1 or MATE2-K [see Pharmacokinetics], such as metformin (see section “Pharmacokinetics”). If co-administration cannot be avoided, drug-related toxicities should be monitored and dosage reduction of the co-administered active substance should be considered if needed.

Effects of other medicinal products on Evrysdi

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

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 significant effect on the pharmacokinetics (PK) of

risdiplam (11% increase in AUC, 9% decrease in Cmax). 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 signal pathway.

Pregnancy, lactation

Male fertility may be compromised while on treatment with Evrysdi based on preclinical study results. In rat and monkey reproductive organs, sperm degeneration and reduced sperm numbers were observed (see section “Preclinical data”).

Prior to initiating treatment with Evrysdi, fertility preservation strategies should be discussed with male patients who are to receive Evrysdi. Male patients may consider sperm preservation prior to treatment initiation. Male patients who wish to father a child should stop treatment with Evrysdi for a minimum of 4 months (see section “Warnings and Precautions”).

Based on preclinical study results, an impact of Evrysdi on female fertility is not expected (see section “Preclinical data”).

The pregnancy status of females of reproductive potential should be verified prior to initiating Evrysdi therapy.

Male and female patients of reproductive potential should adhere to the following contraception requirements:

- Male patients and their female partners, if they are of childbearing potential, should use highly effective contraception during treatment with Evrysdi and for at least 4 months after the last dose.
- Female patients of childbearing potential should use highly effective contraception during treatment with Evrysdi and for at least 1 month after the last dose.

Pregnancy

There are no clinical data from the use of Evrysdi in pregnant women.

Risdiplam has been shown to be embryo-foetotoxic and teratogenic in animal studies. Based on the findings from animal studies, risdiplam crosses the placental barrier and may cause foetal harm (see section “Preclinical data”).

Evrysdi should not be used during pregnancy unless this is clearly required. If a pregnant woman needs to be treated with Evrysdi, she should be clearly advised on the potential risk to the foetus.

Lactation

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

Effects on ability to drive and use machines

The effect of Evrysdi on driving ability or the ability to operate machinery has not been investigated in appropriate studies.

Undesirable effects

The following definitions have been used to classify the frequency of adverse drug reactions: 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); not known (not estimable based on available data).

Summary of the safety profile

In infantile-onset SMA patients, the most common adverse reactions observed in Evrysdi clinical trials were pyrexia (54.8%), rash (29.0%) and diarrhoea (19.4%). In later-onset SMA patients, the most common adverse reactions observed in Evrysdi clinical trials were pyrexia (21.7%), headache (20,0%), diarrhoea (16.7%) and rash (16.7%).
The adverse reactions mentioned above occurred without an identifiable clinical or temporal pattern and generally resolved despite ongoing treatment in infantile-onset and later-onset SMA patients.

Table 3: Summary of adverse drug reactions for infantile-onset and later-onset SMA patients observed in Evrysdi clinical trials

System Organ Class	Infantile-onset SMA[2] (Type 1)	Later-onset SMA[3] (Type 2 and 3)
Gastrointestinal Disorders		
Diarrhoea	Very common	Very common
Nausea	Not applicable	Common
Mouth and aphthous ulcers	Common	Common
Skin and Subcutaneous Tissue Disorders		
Rash[1]	Very common	Very common
Nervous System Disorders		
Headache	Not applicable	Very Common
General Disorders and Adminstration Site Conditions		
Pyrexia (including hyperpyrexia)	Very Common	Very Common
Infections and infestations		
Urinary tract infection (including cystitis)	Common	Common
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	Not Applicable	Common

[1] Includes dermatitis, dermatitis acneiform, dermatitis allergic, erythema, folliculitis, rash, rash erythematous, rash maculo-papular, rash popular.

[2] For infantile-onset SMA patients (FIREFISH Part 1 and 2), adverse reactions are defined as events which occurred in 2% of patients or more and where a causal association with Evrysdi is possible.

[3] For later-onset SMA patients (SUNFISH Part 2), adverse reactions are defined as events which occur at least 2% more frequently in patients treated with Evrysdi compared to placebo during the double-blind placebo controlled period and where a causal association with Evrysdi is possible.

The available safety data are limited in terms of the number of patients exposed to Evrysdi and the length of exposure. There may be potential, relatively rare and potentially serious adverse drug reactions (ADRs) that were undetected during the study programme.

The RAINBOWFISH study provided limited data on safety of Evrysdi for newborns and infants with pre-symptomatic SMA. The RAINBOWFISH study is an ongoing open-label, single-arm study. At the time of interim analysis, the study had included 18 patients who were between 16 and 40 days of age at the time of first administration. The patients weighed between 3.1 and 5.7 kg. The median exposure duration was 8.7 months (range: 0.5 to 22.8 months) (see section Clinical/Efficacy Studies). Based on interim safety, the safety profile of Evrysdi in pre-symptomatic patients appears to be comparable with the safety profile in patients with symptomatic infantile SMA and with later onset patients. No long-term data is available yet.

Safety profile in Patients Previously treated for SMA

The safety profile of Evrysdi for non-naive patients in the JEWELFISH study is consistent with the safety profile for treatment naive SMA patients treated with Evrysdi in the FIREFISH (Part 1 and Part 2), SUNFISH (Part 1 and Part 2) and RAINBOWFISH studies. In the JEWELFISH study, 76 patients previously treated with nusinersen and 14 patients previously treated with onasemnogene abeparvovec were enrolled (see section “Properties/Effects”, Clinical efficacy).

Non-clinical effects

The non-clinical effects on retinal structure, epithelial tissue and haematological parameters described in the section "Preclinical data" have not been observed to date in Evrysdi clinical studies with SMA.

QT Prolongation

A pharmacokinetic/pharmacodynamic analysis showed no evidence of QTc prolongation caused by Evrysdi with exposure in the therapeutic range, but there are no corresponding data at exposure greater than therapeutic levels.

Adverse Reactions from the postmarketing experience

Cutaneous vasculitis was identified during postmarketing experience. Symptoms recovered after permanent discontinuation of Evrysdi. The incidence rate and frequency category cannot be estimated on the basis of the available data.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected new or serious side effect online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

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

Properties/Effects

ATC code

M09AX10

Mechanism of action

Risdiplam is a splicing modifier of SMN2 pre-mRNA (survival of motor neuron 2) for the treatment of SMA which is caused by an SMN protein deficiency as a result of mutations in chromosome 5q. Functional SMN protein deficiency is the pathophysiological mechanism of all SMA types. Risdiplam corrects the splicing of SMN2 and shifts the balance from exon 7 exclusion to exon 7 inclusion into the mRNA transcript leading to an increased production of functional and stable SMN protein. Thus, risdiplam treats SMA by increasing and sustaining functional SMN protein concentrations.

Pharmacodynamics

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 the FIREFISH und SUNFISH clinical trials for infantile-onset SMA and later-onset SMA patients, risdiplam led to a consistent and durable increase in SMN protein with a greater than 2-fold median change from baseline within 4 weeks of treatment initiation as measured in blood. This increase in SMN protein was sustained throughout the treatment period of up to 2 years (see section “Properties/Effects” Clinical efficacy).

Clinical efficacy

The efficacy of Evrysdi for the treatment of SMA patients with infantile-onset (SMA type 1) and later-onset SMA (SMA type 2 and 3) was evaluated in two pivotal clinical studies, FIREFISH and SUNFISH, and supported by additional data from the JEWELFISH study. The efficacy of Evrysdi for the treatment of pre-symptomatic SMA patients was evaluated based on an interim analysis of secondary endpoints of the ongoing RAINBOWFISH study.
Patients with a clinical diagnosis of type 4 SMA have not been studied in clinical trials.

Long-term efficacy for up to two years of treatment has been demonstrated in clinical studies. Beyond two years, only limited data are available.

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 “Dosage/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), 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 (pooled data from Part 1 and Part 2) are shown in Table 4.

Table 4: 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%)
Alive	91.9% (83.9%, 96.1%)	90.3% (81.9%, 94.9%)
Feeding	**N = 58[a]**	
Ability to feed orally[d]	84.5% (74.5%, 91.7%)	82.8% (72.5%, 90.3%)

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 as well feeding, 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.

[d] 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).

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. 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.

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 randomized, double-blind, placebo-controlled confirmatory portion. Patients from part 1 did not take part in part 2.

The primary endpoint was the change from baseline score at Month 12 on the Motor Function Measure-32 (MFM32). The MFM32 has the ability to assess a wide range of motor function across a broad range of SMA patients. The total MFM32 score is expressed as a percentage (0 to 100) of the maximum possible score, with higher scores indicating greater motor function. The MFM32 measures motor function abilities that relate to important daily functions. Small changes in motor function can result in meaningful gain or loss of daily functional ability.

SUNFISH Part 2

SUNFISH Part 2 is the randomized, double-blinded, placebo-controlled portion of the SUNFISH study in 180 non-ambulant patients with type 2 (71%) or type 3 (29%) SMA. Patients were randomized at a 2:1 ratio to receive either Evrysdi at the therapeutic dose (see section “Dosage/Administration”) or placebo. Randomization was stratified by age group (2 to 5, 6 to 11, 12 to 17, 18 to 25 years).

The median age of patients at the start of treatment was 9,0 years old (2-25 years old), the median time between onset of initial SMA symptoms to first treatment was 102,6 (1-275) months. Of the 180 patients included in the trial, 51% were female, 67% were Caucasian and 19% were of Asian descent. At baseline, 67% of patients had scoliosis (32% of patients with severe scoliosis). Patients had a mean baseline MFM32 score of 46,1 and mean Revised Upper Limb Module (RULM) score of 20,1. The overall baseline demographic characteristics were well balanced between the 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 group).

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 summarised in Table 5 and Figure 1.

Table 5: Summary of Efficacy Results in Patients with Later-Onset SMA at Month 12 of Treatment (SUNFISH Part 2)

Endpoint	Evrysdi (N = 120)	Placebo (N = 60)
Primary Endpoint:		
Change from baseline in MFM32 total score[1] at Month 12 LS Mean (95%, CI)	1,36 (0,61; 2,11)	-0,19 (-1,22; 0,84)
Difference from Placebo Estimate (95% CI) p-value[2]	1,55 (0,30; 2,81) 0,0156	
Secondary Endpoints		
Proportion of patients with a change from baseline in MFM32 total score[1] of 3 or more at Month 12 (95% CI)	38,3% (28,9; 47,6)	23,7% (12,0; 35,4)
Odds ratio for overall response (95% CI) Adjusted (unadjusted) p-value[3,4]	2,35 (1,01; 5,44) 0,0469 (0,0469)	
Change from baseline in RULM total score[5] at Month 12 LS Mean (95% CI)	1,61 (1,00; 2.22)	0,02 (-0,8; 0,87)
Difference from Placebo, estimate (95% CI) Adjusted (unadjusted) p-value[2,4]	1,59 (0,55; 2,62) 0,0469 (0,0028)	

LS=least squares

[1] Based on the missing data rule for MFM32, 6 patients were excluded from the analysis (Evrysdi n = 115; placebo control n = 59).

[2] Data analysed using a mixed model with repeated measurements with baseline total score, treatment, visit, age group, treatment-by-visit and baseline value-by-visit.

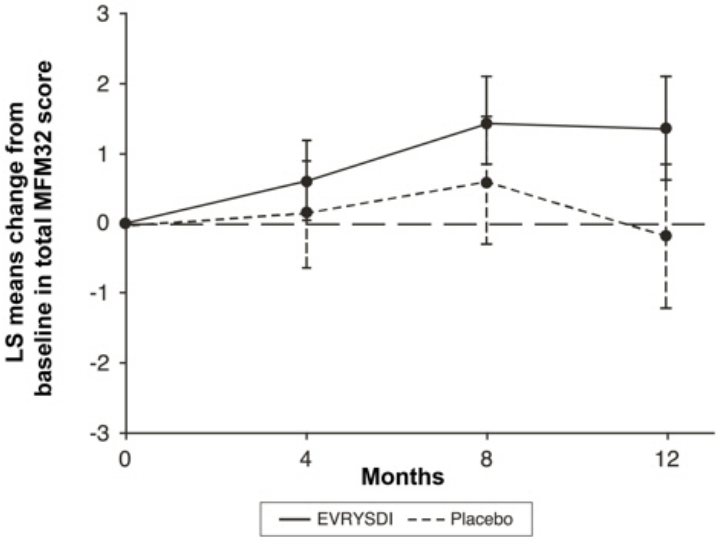
[3] Data analysed using logistic regression for baseline total score, treatment and age group.

[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).

Upon completion of 12 months of treatment, 117 patients continued to received Evrysdi. At the time of the 24 month analysis, these patients who were treated for 24 months experienced further improvement in motor function between month 12 and month 24. The mean change from baseline for MFM32 was 1,83 (CI: 0.74-2.92) and for RULM was 2,79 (CI: 1,94-3,64).

Figure 1: Mean Change (LS) from Baseline in Total MFM32 Score Over 12 months in SUNFISH Part 2



* Error bars denote the 95% confidence interval.
† The MFM total score was calculated according to the user manual, expressed as a percentage of the maximum score possible for the scale (i.e., sum of the 32 item scores divided by 96 and multiplied by 100).

SUNFISH Part 1

The efficacy of Evrysdi in later-onset SMA patients is 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 one year of treatment at the therapeutic dose (the dose selected for part 2), there was a clinically significant 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 two 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 historical cohort with natural disease progression (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 course cohort (after 1 year: 2,7 point difference; p< 0.0001; after two years; 4,0 point difference; p< 0.0001). The natural course cohort experienced a decline in motor function as expected based on the natural progression of SMA (mean change after 1 year: -0,6 points; after 2 years: -2,0 points).

Pre-symptomatic SMA

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

At the time of interim analysis, a total of 18 patients with pre-symptomatic SMA were enrolled in RAINBOWFISH. The preliminary efficacy in pre-symptomatic SMA patients was evaluated in 7 patients who had been treated with Evrysdi for at least 12 months. Of these patients, the median age at first dose was 35 days (range: 16 to 40 days), 71% were female, 100% were Caucasian. Four patients had 2 copies of the *SMN2* gene, 2 patients had 3 copies of the *SMN2* gene, and 1 patient had 4 or more copies of the *SMN2* gene.

At the time of the interim analysis, patients with 2 or 3 copies of SMN2 (N = 6) achieved the following HINE-2 motor milestones in month 12: 6 (100%) patients could sit (5 patients could turn themselves and 1 patient achieved stable sitting), 4 (67%) patients could stand (3 patients could stand unaided and 1 patient could stand with assistance) and 3 (50%) patients could walk independently.

Use in previously treated SMA patients

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 other SMA therapies (including nusinersen and onasemnogene abeparvovec). As of 31 July 2020, of the 173 patients that received Evrysdi, 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 compared to baseline after 4 weeks of Evrysdi treatment.

Pharmacokinetics

Pharmacokinetic parameters for risdiplam have been characterized 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. The PK of risdiplam is best described by a population PK model with resorption via three transit compartments, two-compartment disposition and elimination with first-order kinetics. Body weight and age were found to have significant effects on the PK.

The estimated exposure (mean $AUC_{0\text{-}24h}$) for infantile-onset SMA patients (age 2-7 months at enrolment) at the therapeutic dose of 0,2 mg/kg once daily was 1930 ng.h/ml. In pre-symptomatic

infants aged between 16 days and 2 months, the mean estimated exposure in the RAINBOWFISH study after 2 weeks of one daily dose of 0.15 mg/kg was 2080 ng.h/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.h/ml. The observed maximum concentration (mean Cmax) was 194 ng/ml at 0,2 mg/kg in FIREFISH and 120 ng/mL in SUNFISH part 2 and the mean estimated maximum concentration at 0.15 mg/kg in RAINBOWFISH is 113 ng/ml.

Absorption

Risdiplam was rapidly absorbed in the fasted state with a plasma tmax ranging from 1 to 4 hours after oral administration.

In the clinical studies, risdiplam was administered with a morning meal or after breastfeeding.

Distribution

The population pharmacokinetic parameter estimates were 98 l for the apparent central volume of distribution, 93 l for the peripheral volume, and 0,68 l/hour for the inter-compartmental 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 primarily metabolized by flavin monooxygenases 1 and 3 (FMO1 and FMO3), and also by CYP isoenzymes 1A1, 2J2, 3A4 and 3A7. Parent drug was the major component found in plasma, accounting for 83% of active substance related material in circulation. The pharmacologically inactive metabolite M1 was identified as the major circulating metabolite.

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.

Approximately 53% of the dose (14% in the form of unaltered risdiplam) was excreted in the feces and 28% in urine (8% as unaltered risdiplam).

Hepatic impairment

Mild and moderate hepatic impairment had no impact on the PK of risdiplam. After administration of 5 mg risdiplam, the mean ratios for Cmax and AUC were 0,95 and 0,80 in mild (n = 8) and 1,20 and

1,08 in moderate hepatically impaired subjects (n = 8) versus matched healthy controls (n = 10). The safety and PK in patients with severe hepatic impairment have not been studied to date.

Renal impairment

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

Elderly patients

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.

Children and adolescents

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.

Ethnic origin

The PK of risdiplam does not differ in person of Japanese and Caucasian descent.

Preclinical data

Genotoxicity

Risdiplam was not mutagenic in a bacterial reverse mutation assay. In mammalian cells *in vitro* and in bone marrow of rats, risdiplam increases the frequency of micronucleated cells. Micronucleus induction in bone marrow was observed in several toxicity studies in rats (adult and juvenile animals). The no observed adverse effect level (NOAEL) across the studies was 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. The same effect is also manifested in other tissues with high cell turnover with changes in the skin, gastrointestinal tract, male germ cells, bone marrow, as well as embryonal toxicity. Risdiplam does not possess a potential to damage DNA directly.

Carcinogenicity

A 2-year carcinogenicity study in rats is ongoing. A carcinogenicity study with risdiplam in rasH2 transgenic mice did not give any evidence for a tumorigenic potential of risdiplam with animals exposed up to 7-fold the exposure in humans at the therapeutic dose.

Reproductive toxicity

In studies in pregnant rats treated with risdiplam, embryofoetal toxicity with reduced foetal weight and delayed development was evident. The NOAEL dose 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, embryo-foetal mortality and dysmorphogenic effects were observed at exposures also associated with maternal toxicity. Four foetuses (4%) from 4 litters (22%) developed hydrocephalus. The NOAEL dose for this 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 duration. No adverse effects were recorded on the survival, growth, functional (behavioural or reproductive) performance of the offspring.

Studies in pregnant rats showed that risdiplam crosses the placental barrier and is transferred into the milk.

Other data

Treatment with risdiplam has been associated with cell cycle arrest in male germ cells in rats and monkeys. These effects led to degenerated spermatocytes, degeneration/necrosis of the seminiferous epithelium, and oligo/aspermia in the epididymis. In young rats, effects were seen at exposure levels reached at the therapeutic dose of risdiplam in patients. However, there was no impairment on male fertility seen in a respective study in rats. Sperm cell effects of risdiplam are likely related to an interference of risdiplam with the cell cycle of dividing cells and are stage specific and reversible. No effects were seen on female reproductive organs in rats and monkeys after treatment with risdiplam.

Effect on retinal structure

Chronic treatment of monkeys with risdiplam yielded evidence for an effect on the retina in terms of photoreceptor degeneration starting in the periphery of the retina. Upon cessation of treatment, the effects in the retinogram were partially reversible but the photoreceptor degeneration was not reversible. The effects were monitored by optical coherence tomography (OCT) and by electroretinography (ERG). The effect occurred with an exposure in excess of two times the exposure in humans at the therapeutic dose.

Effect on epithelial tissues

Effects on skin, larynx and eyelid histology and the gastrointestinal tract (GI) tract were evident in rats and monkeys treated with risdiplam. Changes started to be seen with treatment of 2 weeks and longer at more than 2-fold the human exposure). With chronic treatment for 39 weeks in monkeys, the NOAEL was at an exposure of about 2-times the average exposure in humans at the therapeutic dose

Effect on hematological parameters

In the acute bone marrow micronucleus test in rats, a reduction of more than 50% in the ratio of polychromatic (young) to normochromatic (adult) erythrocytes, indicative of substantial bone marrow toxicity, was observed at the high dose level with exposure in excess of 15-times the average exposure in humans at the therapeutic dose. With longer treatment of rats for 26 weeks, the exposure margins to the NOAEL were approximately four times the average exposure in humans at the therapeutic dose.

Juvenile animal studies

Risdiplam was studied for toxicity with chronic administration in rats and monkeys. Studies in juvenile animals showed reduced food intake, slower growth and signs of toxicity in reproductive organs at an exposure to similar to the therapeutic dose for humans.
In terms of toxicity seen after treatment with risdiplam in various organ systems with high cell turnover (skin, GI-tract, bone marrow), animal studies do not indicate any differences in sensitivity between juvenile, adolescent and adult animals.

Other information

Incompatibilities

No incompatibilities between Evrysdi and the recommended reusable syringes for oral administration have been observed.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Shelf life after opening

The ready-to-use solution is stable for 64 days when stored in the refrigerator (2 °C to 8 °C).

Special precautions for storage

Powder:
Keep the container in the outer carton in order to protect the contents from light (and moisture).

Do not store above 25 °C.

Ready-to-use oral solution:
Keep the container in the outer carton in order to protect the contents from light.
Store in the refrigerator (2-8 °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 store the oral solution above 40 °C.
Keep the bottle tightly closed and always store in an upright position.

Keep out of the reach of children.

Instructions for handling

- Instructions to observe before, during and after the preparation of the oral solution: The solution must always be prepared by a healthcare professional (e.g. physician or pharmacist).
- Avoid inhaling EVRYSDI powder. Take notice of local regulations and use suitable equipment to prepare the Evrysdi solution.
- Wear gloves.
- Do not use the powder if the expiry date has passed. The expiry date of the powder is printed on the bottle label.
- Do not dispense the reconstituted solution if the “Ready-to-use oral solution. **Expiry date**”- date which is stated on the bottle label and folding box exceeds the original powder expiration date.
- Avoid any contact with the medicine on your skin. If the medicine (powder or solution) gets on your skin, wash the area with water and soap.
- Do not use the medicine if any of the contents of the package are damaged or missing.
- Use purified water or water for injection to prepare the solution.
- Do not add oral syringes other than the ones provided in the carton.
- Do not mix Evrysdi into food or liquids (eg. milk or formula milk).
- Do not mix Evrysdi from the new bottle with the bottle you are currently using.

The patient, respectively, care giver must be instructed by a healthcare professional how the prescribed daily dose is to be prepared and administered before delivery of the prepared solution. (Instructions for use for Evrysdi can be found in the package).

Preparation of the oral solution

Pour 79 ml of purified water or water for injection into the bottle with medication.

Insert the press-in bottle adapter into the opening by pushing it down.

After completely closing the bottle, shake for 15 seconds.

After waiting for 10 minutes, a clear solution should be obtained. If not, shake well again for another 15 seconds.

The “Ready-to-use oral solution. **Do not use after”-date 64 days** after preparation of the solution should be calculated. The day of preparation of the solution is counted as day 0.

The calculated date should be entered on the label of the bottle in the field provided for this purpose under "Ready-to-use oral solution. **Do not use after** (DD.MM.YYYY)" and additionally on the designated field on the outer carton.

For a more detailed description, instructions for preparation for the doctor or pharmacist are included in the package.

Disposal of unused/expired medicines

The release of pharmaceuticals into the environment must be kept as low as possible. Medicines must not be disposed of via wastewater and disposal through household waste should be avoided.

Unused/expired medicines should be disposed of professionally by the dispensing point (doctor or pharmacist).

Marketing authorisation number

67251 (Swissmedic).

Packs

1 bottle containing powder for 80 ml oral solution (0,75 mg/ml risdiplam) [A].
The package also contains one press-in bottle adapter, two reusable 1 ml oral syringes two reusable 6 ml oral syringes and one reusable 12 ml oral syringe.

Marketing authorisation holder

Roche Pharma (Schweiz) AG, Basel.

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