Evrysdi®
Pulver zur Herstellung einer Lösung zum Einnehmen
Zul.-Nr. 67251

Public Risk Management Plan (RMP) Summary

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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of “Evrysdi” is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of “Evrysdi” in Switzerland is the “Arzneimittelinformation/ Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. “Roche Pharma (Schweiz) AG” is fully responsible for the accuracy and correctness of the content of the published summary RMP of “Evrysdi”.

PART VI: SUMMARY OF THE RISK-MANAGEMENT PLAN

Summary of Risk Management Plan for EVRYSDI (RISDIPLAM)

This is a summary of the risk-management plan (RMP) for Evrysdi. The RMP details important risks of Evrysdi, how these risks can be minimized, and how more information will be obtained about Evrysdi's risks and uncertainties (missing information).

Evrysdi's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Evrysdi should be used.

This summary of the RMP for Evrysdi should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Evrysdi's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Evrysdi is authorized for the treatment of 5q spinal muscular atrophy (SMA) in patients 16 days of age and older, with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four *SMN2* copies (see SmPC for the full indication). It contains risdiplam as the active substance, and it is given as a solution by mouth or feeding tube.

Further information about the evaluation of Evrysdi's benefits can be found in Evrysdi's EPAR, including in its plain-language summary, available on the EMA Web site, under the medicine's Web page:

https://www.ema.europa.eu/en/medicines/human/EPAR/evrysdi

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Evrysdi, together with measures to minimize such risks and the proposed studies for learning more about Evrysdi's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorized pack size—The amount of medicine in a pack is chosen so as to ensure that the medicine is used correctly.
- The medicine's legal status—The way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Evrysdi is not yet available, it is listed under “missing Information” below.

II.A List of Important Risks and Missing Information

Important risks of Evrysdi are risks that need special risk-management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Evrysdi. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information about the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	Retinal toxicity Embryofetal toxicity Effect on epithelial tissues
Missing information	Long-term safety

II.B Summary of Important Risks

Important Potential Risk: Retinal toxicity	
Evidence for linking the risk to the medicine	In the chronic 39-week toxicity study in monkeys, multifocal peripheral retinal degeneration in the photoreceptor layer and microcystic spaces in the inner retinal layers (Microcystic macular degeneration, MMD) was detected by spectral domain-optical coherence tomography (sdOCT). This was associated with depressed scotopic (rod) B-wave and somewhat less affected photopic (cone) B-wave in the electroretinogram (ERG). Retinal findings were observed after a delay of 2-5 months. These findings were confirmed by histopathology and did not appear to impair vision of the animals (based on general behavior and ophthalmology assessments). The MMD and depressed ERG almost fully recovered in the 22-week recovery phase of the monkey study but the peripheral photoreceptor loss and hyperreflective/hypertrophic RPE did not. No retinal changes were observed in monkeys associated with an exposure in the range of the exposure at the clinical dose of risdiplam. No retina changes were seen in 2-week monkey toxicity study. In albino and pigmented rats treated for 26 weeks, no retinal changes were detected despite higher exposure and even more pronounced melanin binding compared to monkeys. Both irreversible photoreceptor loss in the retinal periphery and reversible microcystoid spaces in the inner nuclear layer were clearly detectable by sdOCT with high sensitivity and correlated well with histopathological findings. Peripheral photoreceptor loss was detected by sdOCT at lower doses than changes were detected by ERG. Hence, it appears that structural damage can be detected by sdOCT at lower doses than functional changes detectable by ERG. Thus, primarily sdOCT has been chosen as a suitable means of monitoring onset, severity and progress of retinal findings induced by risdiplam in monkeys and can be used for this purpose also in SMA patients.
Risk factors and risk groups	Retinal toxicity has not been observed in humans therefore risk factors and risk groups cannot be identified in humans and must be extrapolated from nonclinical studies. Since the patho-mechanism of the retinal toxicity of risdiplam in monkeys has not been fully elucidated, contributing risk factors are unknown. The potential for synergistic effects of concomitant administration of risdiplam with other retinotoxic drugs has not been studied in nonclinical and clinical studies. Significant overdoses over several months may be considered as risk factors for retinal toxicity based on the exposure dependency of findings in the nonclinical monkey study. Overdoses are a potential risk factor for retinal toxicity in the clinical setting

Important Potential Risk: Retinal toxicity	
Risk-minimization measures	**Routine risk minimization measures:** • Section 4.4 of the SmPC (Special warnings and precautions for use) • Section 5.3 of the SmPC (Preclinical safety data; Effect on retinal structure) **Routine risk-minimization activities recommending specific clinical measures to address the risk:** Section 4.5 of the SmPC (Interaction with other medicinal products and other forms of interaction) **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Risdiplam is a medicinal product subject to restricted medical prescription. **Additional risk-minimization measures:** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** OLE until 5 years of treatment for all patients in following studies: Study BP39056 (FIREFISH) Study BP39055 (SUNFISH) Study BP39054 (JEWELFISH) Study BN40703 (RAINBOWFISH) **See Section II.C of this summary for an overview of the post-authorization development plan.**
Important Potential Risk: Embryofetal toxicity	
Evidence for linking the risk to the medicine	Consistent with its effects on cell division and apoptosis, treatment of pregnant rabbits with risdiplam has been associated with maternal toxicity and teratogenicity, with a NOAEL at exposures of ~4 times the mean exposure guidance in clinical trials. No teratogenicity was observed in rats up to ~5 times the clinical mean exposure guidance, but embryofetal toxicity (reduced fetal weight and delayed fetal development) was noted, with a NOAEL slightly in excess of 2-fold the mean exposure guidance without maternal toxicity. Even though teratogenicity was only noted in the rabbit at a maternally toxic dose level, the possibility of a dysmorphogenic potential of risdiplam in the human cannot be discounted.
Risk factors and risk groups	Women who have been exposed to risdiplam during pregnancy or 1 month prior to the start of pregnancy

Important Potential Risk: Retinal toxicity	
Risk-minimization measures	**Routine risk minimization measures:** • SmPC Section 4.4 (Special warnings and precautions for use) • SmPC Section 4.6 (Fertility, pregnancy and lactation) • SmPC Section 5.3 (Preclinical safety data) • Section 2 of the Package Leaflet (What you need to know before you or your child take Evrysdi; Pregnancy, contraception, breastfeeding and male fertility) **Routine risk-minimization activities recommending specific clinical measures to address the risk:** • SmPC Section 4.6 (Fertility, pregnancy and lactation)
	Other risk minimization measures beyond the Product Information: Medicine's legal status: Risdiplam is a medicinal product subject to restricted medical prescription. **Additional risk-minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study BN42833 Risdiplam Pregnancy Surveillance Study **See Section II.C of this summary for an overview of the post-authorization development plan.**

Important Potential Risk: Effect on Epithelial tissues	
Evidence for linking the risk to the medicine	In chronic toxicology studies in rodents and monkeys, adverse effects on epithelial tissues (skin, larynx, eyelid, and gastrointestinal tract) were observed. These effects were observed within days or weeks of treatment, were dose-dependent in severity, and occurred with high incidence. The first clinical sign in monkeys was mild parakeratosis at exposures more than 2.5-fold the exposure observed at the pivotal dose selected for patients with SMA. These findings were reversible upon discontinuation of dosing with risdiplam but persisted with continuous dosing and worsened at high doses with breakage of the skin barrier when animals were dosed through.
Risk factors and risk groups	Risk factors and risk groups: Skin events suggestive of effects on epithelial tissues have not been observed in humans therefore risk factors and risk groups cannot be identified in humans and must be extrapolated from nonclinical studies. Overdoses are a potential risk factor for effects on epithelial tissues based on findings in the nonclinical studies.
Risk-minimization measures	**Routine risk minimization measures:** • Section 5.3 of the SmPC (Preclinical safety data; Effect on epithelial tissues) **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Risdiplam is a medicinal product subject to restricted medical prescription. **Additional risk-minimization measures:** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** OLE until 5 years of treatment for all patients in following studies: • Study BP39056 (FIREFISH) • Study BP39055 (SUNFISH) • Study BP39054 (JEWELFISH) • Study BN40703 (RAINBOWFISH) **See Section II.C of this summary for an overview of the post-authorization development plan.**

Missing Information: Long-term safety	
Risk-minimization measures	**Other risk minimization measures beyond the Product Information:** Medicine's legal status: Risdiplam is a medicinal product subject to restricted medical prescription. No additional risk-minimization measures
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study BP42817 (QTc Study) OLE until 5 years of treatment for all patients in following studies: • Study BP39056 (FIREFISH) • Study BP39055 (SUNFISH) • Study BP39054 (JEWELFISH) • Study BN40703 (RAINBOWFISH) **See Section II.C of this summary for an overview of the post-authorization development plan.**

II.C Post-Authorization Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorization

The following studies are conditions of the marketing authorization.

Study short name: Non Interventional Post-Authorization Efficacy Study (PAES) BN43428

Purpose of the study

A long-term prospective, observational study to further evaluate disease progression in SMA patients (both pre-symptomatic and symptomatic) with 1 to 4 *SMN2* copies treated with risdiplam, in comparison to natural history data in untreated patients.

II.C.2 Other Studies in Post-Authorization Development Plan

Study short name: Study BP39056 (FIREFISH) Open-Label Extension

Purpose of the study

Continued general safety as well as ophthalmological monitoring and effects on epithelial tissues in the OLE phase of ongoing clinical studies in SMA patients will occur for treatment duration of 5 years (study duration of 2 years, followed by 3 years OLE). Any evidence of delayed retinal toxicity beyond 2 years of treatment will be reported as part of routine PSUR/PBRER assessments until completion of the OLE phases of the risdiplam studies. This comprehensive monitoring with independent central assessment will provide a comprehensive dataset to evaluate retinal toxicity and long-term safety.

Study short name: Study BP39055 (SUNFISH) Open-Label Extension

Purpose of the study

Continued general safety as well as ophthalmological monitoring and effects on epithelial tissues in the OLE phase of ongoing clinical studies in SMA patients will occur for treatment duration of 5 years (study duration of 2 years, followed by 3 years OLE). Any evidence of delayed retinal toxicity beyond 2 years of treatment will be reported as part of routine PSUR/PBRER assessments until completion of the OLE phases of the risdiplam studies. This comprehensive monitoring with independent central assessment will provide a comprehensive dataset to evaluate retinal toxicity and long-term safety.

Study short name: Study BP39054 (JEWELFISH) Open-Label Extension

Purpose of the study

Continued general safety as well as ophthalmological monitoring and effects on epithelial tissues in the OLE phase of ongoing clinical studies in SMA patients will occur for treatment duration of 5 years (study duration of 2 years, followed by 3 years OLE). Any evidence of delayed retinal toxicity beyond 2 years of treatment will be reported as part of routine PSUR/PBRER assessments until completion of the OLE phases of the risdiplam studies.

This comprehensive monitoring with independent central assessment will provide a comprehensive dataset to evaluate retinal toxicity and long-term safety.

Study short name: Study BN40703 (RAINBOWFISH) Open-Label Extension

Purpose of the study

Continued general safety as well as ophthalmological monitoring and effects on epithelial tissues in the OLE phase of ongoing clinical studies in SMA patients will occur for treatment duration of 5 years (study duration of 2 years, followed by 3 years OLE). Any evidence of delayed retinal toxicity beyond 2 years of treatment will be reported as part of routine PSUR/PBRER assessments until completion of the OLE phases of the risdiplam studies. This comprehensive monitoring with independent central assessment will provide a comprehensive dataset to evaluate retinal toxicity and long-term safety.

Study short name: Study BN42833 (Risdiplam Pregnancy Surveillance Study)

Purpose of the study

To collect and describe selected pregnancy outcomes (i.e., live birth, spontaneous abortions, stillbirths, elective abortions, and preterm births) and pregnancy complications in women with SMA exposed to risdiplam during the defined exposure window.

To collect and describe selected fetal/neonatal/infant outcomes (i.e., major and minor congenital malformations, small for gestational age, and postnatal growth and development) at birth and through up to the first year of life of infants born to women exposed to risdiplam during the defined pregnancy exposure window.

Study short name: Study BP42817 (QTc Study)

Purpose of the study

To estimate the effects of single oral doses of risdiplam on QT interval of the ECG (QT)/QT corrected for heart rate (QTc) interval in healthy subjects.