Summary of the Risk Management Plan for Orladeyo®

Orladeyo (berotralstat)

Marketing Authorisation Holder:

BioCryst Schweiz GmbH

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Disclaimer

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 ORLADEYO 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 ORLADEYO in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic.

BioCryst Schweiz GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of ORLADEYO.

Summary of Risk Management Plan for ORLADEYO (berotralstat)

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

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

This summary of the RMP for Orladeyo 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 Orladeyo's RMP.

I. The medicine and what it is used for

Orladeyo is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older. It contains berotralstat as the active substance and it is taken orally once a day.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

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

Measures to minimise 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 authorised pack size - the amount of medicine in a pack is chosen 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 minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed 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 berotralstat is not yet available, it is listed under 'missing information' below.

a. List of important risks and missing information

Important risks of berotralstat are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 berotralstat. 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 on 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).

Table 1: List of Important Risks and Missing Information

Important identified risks	none
Important potential risks	Hypersensitivity Hepatotoxicity QT Prolongation Carcinogenicity Phospholipidosis Drug-drug interaction with narrow therapeutic index drugs metabolised by CYP2D6 and CYP3A4
Missing information	Safety profile in pregnancy and lactation Long-term safety in paediatric patients

b. Summary of important risks

Table 2: Important Potential Risk: Hypersensitivity

Evidence for linking the risk to the medicine	During nonclinical development, no hypersensitivity or skin rashes were noted in any animal species dosed. Delayed-type hypersensitivity rash was identified as an event of special interest (EOSI) during initial Phase 1 studies in healthy subjects, but few events have been reported in patients with HAE, and these were mild to moderate, self-limited, and not dose dependent. The rashes resolved in all subjects. Most subjects continued dosing with berotralstat without interruption, and the rashes did not reoccur with continued dosing, or in cases where dosing was interrupted, when berotralstat was restarted.
Risk factors and risk groups	Patients with hypersensitivity to the active substance or any of the excipients in berotralstat are at increased risk. There is no association with human leukocyte antigen (HLA) type or other comorbidity.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.3, 4.8 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Prescribing Information: Legal status: medical prescription Additional risk minimisation measures: none
Additional pharmacovigilance activities	Post-authorisation Study 401 (see Section II.C)

Table 3: Important Potential Risk: Hepatoxicity

Evidence for linking the risk to the medicine	The liver was considered a target organ in toxicology studies due to reversible, non-adverse transaminase elevations seen in monkeys dosed for 39 weeks, along with hepatocellular hypertrophy. In rats, there were no enzyme elevations but there was extrahepatic and liver bile duct hyperplasia and phospholipidosis (PLD). In humans, alanine transaminase (ALT) elevations and, to a lesser degree, aspartate transaminase (AST) elevations > 3 × upper limit of normal (ULN) have been seen in clinical trials of subjects with HAE, but no clinical signs of jaundice, synthetic liver dysfunction, or liver injury have been reported and no subject met the criteria for Hy's Law. The association is not clear because transaminase elevations were not seen in the absence of prior androgen exposure, particularly very recently exposure.
Risk factors and risk groups	An association between prior androgen use and asymptomatic elevations in ALT was identified. More important than life-time exposure was recent abrupt discontinuation of androgens. Prior androgen use is high in patients with HAE. In the long-term safety trials, 63.2% of subjects had prior androgen use.
Risk minimisation measures	Routine risk minimisation measures: Summary of product characteristics (SmPC) Section 4.8 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Prescribing Information: Legal status: medical prescription Additional risk minimisation measures: none
Additional pharmacovigilance activities	Post-authorisation Study 401 (see Section II.C)

Table 4: Important Potential Risk: QT Prolongation

Evidence for linking the risk to the medicine	Studies in nonhuman primate (NHP) showed quantitatively small drug-related prolongation of the QT interval. A thorough QT study was conducted and showed that at steady state, the maximum observed plasma concentration (C_{max}) of berotralstat at the recommended dose of 150 mg once daily resulted in a mean corrected QT (QTc) increase of 3.4 msec (90% confidence interval upper bound [UB] of 6.8 msec), which is below the 10 msec threshold for regulatory concern. Exposures 4-fold higher than achieved at the recommended dose increased the QTc by 21.9 msec (mean). Based on exposure-response modelling, at the highest anticipated clinically relevant exposure in a worst-case scenario of geometric mean C_{max} of 240 ng/mL, in the setting of hepatic impairment (moderate and severe hepatic failure, Pugh-Child class B and C), the estimated ΔΔQTcF was 7.0 msec (2-sided 90% UB 10.9 msec). These values exceed the ICH E14 threshold for potential clinical significance. It should be noted that in Study BCX7353-108, conducted in subjects who had varying degrees of hepatic failure including moderate and severe, no clinically significant ECG changes were observed, no subject had a change from baseline in QTcF > 30 msec, and no subject had a QTcF > 500 msec. The study was single dose so the risk cannot be confirmed. Subjects with moderate to severe hepatic failure were not enrolled in the long-term prophylactic clinical trials and this potential effect is based only on modelling. Additionally, low body weight could increase berotralstat exposures. Adolescents and adults weighing < 40 kg were excluded from the development program. As weight is the primary covariate affecting pharmacokinetics (PK) in the population PK model, modelling indicates that at lower weights, berotralstat exposure is higher than at higher weights. Exposures in patients weighing 40 kg do not exceed concentrations at which there is a concern for prolonged QT.

	Modelling indicates that at lower weights, around 35 kg, patients are simulated to have C_{max} exposure of approximately 222 ng/mL, the concentration at which the 2-sided 90% UB for ΔΔQTcF is 10 msec. There are no clinical data in subjects weighing < 40 kg, and it is appropriate to restrict use of berotralstat in these subjects. No dose adjustment is required for patients weighing at least 40 kg. An additional analysis of the QT sub-intervals revealed that multiple supratherapeutic daily doses of berotralstat prolonged the QTc interval but had little effect on the J to T peak sub-interval, which suggests that the QT prolongation reported with berotralstat can be categorised as "benign" and unlikely to be associated with proarrhythmic risk, similar to marketed drugs ranolazine or verapamil. No subject in the 3 long-term prophylaxis studies (204, 301, and 302) experienced clinically significant QT prolongation.
Risk factors and risk groups	Patients with moderate or severe (Child-Pugh Class B and C) liver failure Patients with weight < 40 kg Patients with independent risk factors for QT prolongation Extrinsic: • electrolyte disturbances • concomitant use of other drugs known to either prolong the QTc or increase berotralstat drug levels (e.g., cyclosporine). Intrinsic: • congenital QT prolongation • acquired QT prolongation • advanced age
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, 5.3

	Routine risk minimisation activities recommending specific clinical measures to address the risk: Use of berotralstat in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) should be avoided Use of berotralstat in patients weighing < 40 kg should be avoided It is preferable to avoid the use of berotralstat in patients with severe renal impairment Appropriate monitoring for patients with independent risk factors for QT prolongation should be considered Other routine risk minimisation measures beyond the Prescribing Information: Legal status: medical prescription Additional risk minimisation measures: none
Additional pharmacovigilance activities	Post-authorisation Study 401 (see Section II.C)

Table 5: Important Potential Risk: Carcinogenicity

Evidence for linking the risk to the medicine	Rare stromal sarcomas of the endometrium and undifferentiated sarcomas of the skin were found in a 2-year (lifetime) study in rats administered berotralstat at an exposure that was 4.5 times the exposure achieved (on an AUC basis) at the clinical 150 mg berotralstat dose. These findings are inconclusive, with an incidence slightly higher than in control groups. The clinical relevance of these findings is unknown. Across the berotralstat clinical development program, there was no evidence of carcinogenicity. Nevertheless, carcinogenicity is addressed as an important potential risk.
Risk factors and risk groups	Unknown
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Prescribing Information: Legal status: medical prescription Additional risk minimisation measures: none
Additional pharmacovigilance activities	Post-authorisation Study 401

Table 6: Important Potential Risk: Phospholipidosis

Evidence for linking the risk to the medicine	Toxicity studies of berotralstat in rats and monkeys demonstrated the presence of foamy and/or vacuolated macrophages in several tissues and organs of both rats and monkeys, including liver, lung, small intestine, spleen, and lymph nodes.
Risk factors and risk groups	Unknown The lack of any clinical evidence of PLD occurring in humans as well as the inconclusive evidence that PLD is detrimental, the benefit-risk impact is considered minimal.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Prescribing Information: Legal status: medical prescription Additional risk minimisation measures: none
Additional pharmacovigilance activities	Post-authorisation Study 401

Table 7: Important Potential Risk: Drug-Drug Interaction with Narrow Therapeutic Index Drugs Metabolised by CYP2D6 and CYP3A4

Evidence for linking the risk to the medicine	Drug-drug interaction studies with various doses of berotralstat.
Risk factors and risk groups	Patients taking berotralstat concomitantly with drugs metabolised by CYP2D6 or CYP3A4.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.5, 5.2 Routine risk minimisation activities recommending specific clinical measures to address the risk: For concomitant medicines that are predominantly metabolised by CYP2D6 (e.g., thioridazine, pimozide) or CYP3A4 (e.g., cyclosporine, fentanyl), particularly those with a narrow therapeutic index, dose adjustments of these medicines may be required (SmPC Section 4.5) Other routine risk minimisation measures beyond the Prescribing Information: Legal status: medical prescription Additional risk minimisation measures: none

Table 8: Missing Information: Safety Profile in Pregnancy and Lactation

Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.6, 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: Berotralstat is not recommended during pregnancy and use during lactation should take individual benefit-risk into consideration. Other routine risk minimisation measures beyond the Prescribing Information: Legal status: medical prescription Additional risk minimisation measures: none

Table 9: Missing Information: Long-term Safety in Paediatric Patients

Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Prescribing Information: Legal status: medical prescription Additional risk minimisation measures: none
Additional pharmacovigilance activities	Post-authorisation Study 401

c. Post-authorisation development plan

i. Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation.

ii. Other studies in the post-authorisation development plan

Table 10: Other Studies in the Post-Authorisation Development Plan

Study Name	Purpose of the Study
PASS 401: Non-Interventional Post-Authorisation Study to Evaluate Safety, Tolerability and Effectiveness of Berotralstat for Patients with Hereditary Angioedema (HAE) in a Real-World Setting	As the long-term safety cannot be addressed during clinical trials, this non-interventional post-authorisation safety study (NI-PASS) is designed to further characterise the safety profile of berotralstat. The long-term impact of berotralstat administration on the growth of adolescent participants is of particular interest. Study BCX7353-401 is a prospective NI-PASS to evaluate the long-term safety, tolerability, and effectiveness of berotralstat in HAE patients receiving berotralstat for long-term prophylaxis. Primary objective: To monitor safety and tolerability of berotralstat for routine prevention of attacks of hereditary angioedema in adult and adolescent patients during long-term administration in a real-world setting Secondary objectives: • To evaluate the effectiveness of berotralstat for routine prevention of attacks of hereditary angioedema in adult and adolescent patients in a real-world setting • To assess quality of life during long-term administration of berotralstat in a real-world setting • To assess growth and development in adolescent patients 12 to 17 years of age