Date: 8 July 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Orladeyo

International non-proprietary name: berotralstat
Pharmaceutical form: hard capsules
Dosage strength(s): 150 mg
Route(s) of administration: oral
Marketing Authorisation Holder: BioCryst Schweiz GmbH
Marketing Authorisation No.: 68464
Decision and Decision date: approved on 7 June 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
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	U.S. Food and Drug Administration
GLP	Good Laboratory Practice
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 pharmacokinetic
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
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)

New Active Substance status
The applicant requested the status of a new active entity for the active substance berotralstat of the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 2 of the TPA. The Orphan Drug Status was granted on 22 June 2021.

Authorisation human medical product under Art. 13 TPA
The applicant requested a reduced assessment procedure in accordance with Art. 13 TPA.

2.2 Indication and Dosage

2.2.1 Requested Indication

Orladeyo is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.

2.2.2 Approved Indication

Orladeyo is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.

2.2.3 Requested Dosage

Summary of the applied standard dosage:

The recommended dose for adults and adolescents aged 12 years and older weighing ≥ 40 kg is 150 mg berotralstat once daily.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	22 July 2021
Formal control completed	20 August 2021
Predecision	9 December 2021
Answers to Predecision	25 February 2022
Final Decision	7 June.2022
Decision	approval

Swissmedic has not assessed the primary data of this application and relies for its decision on the assessment of the foreign reference authority European Medicines Agency (EMA). The current SwissPAR refers to the publicly available EMA Assessment Report for Orladeyo, published 1 June 2021, Procedure No. EMEA/H/C/005138/0000.

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3 Quality Aspects

Swissmedic has not assessed the primary data relating to quality aspects of this application and is taking over the results of the assessment of the foreign reference authority European Medicines Agency (EMA). The current SwissPAR relating to quality aspects refers to the publicly available EMA Assessment Report for Orladeyo, published 1 June 2021, Procedure No. EMEA/H/C/005138/0000.

4 Nonclinical Aspects

Swissmedic has not assessed the primary data relating to preclinical aspects of this application and is taking over the results of the assessment of the foreign reference authority European Medicines Agency (EMA). The current SwissPAR relating to preclinical aspects refers to the publicly available EMA Assessment Report for Orladeyo, published 1 June 2021, Procedure No. EMEA/H/C/005138/0000.

5 Clinical and Clinical Pharmacology Aspects

Swissmedic has not assessed the primary data relating to clinical aspects of this application and relies on the assessment of the foreign reference authority European Medicines Ageny (EMA). The current SwissPAR relating to clinical aspects refers to the publicly available EMA Assessment Report for Orladeyo, published 1 June 2021, Procedure No. EMEA/H/C/005138/0000.

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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 Orladeyo, hard capsules 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.

Orladeyo® 150 mg hard capsules

Composition

Active substances

Berotralstat (as berotralstat dihydrochloride)

Excipients

Pregelatinised starch, crospovidone (type A), colloidal anhydrous silica, magnesium stearate
Capsule shell: Gelatin, titanium dioxide, indigo carmine, black iron oxide, red iron oxide
Printing ink: Shellac, propylene glycol, potassium hydroxide, black iron oxide.

Pharmaceutical form and active substance quantity per unit

Each hard capsule contains 150 mg berotralstat (as dihydrochloride).
Capsule (19.4 mm × 6.9 mm) with white opaque body imprinted with “150” and light blue opaque cap imprinted with “BCX”.

Indications/Uses

Orladeyo is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.

Dosage/Administration

Usual dosage

The recommended dose for adults and adolescents aged 12 years and older weighing ≥ 40 kg is 150 mg berotralstat once daily.
Orladeyo is not intended for treatment of acute HAE attacks (see section "Warnings and precautions").

Special dosage instructions

Patients with hepatic disorders

No dose adjustment is required for patients with mild hepatic impairment. Use of berotralstat in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) should be avoided (see section "Pharmacokinetics").

Patients with renal disorders

No dose adjustment is required for patients with mild or moderate renal impairment. In patients with severe renal impairment, it is preferable to avoid the use of berotralstat. If treatment is required, appropriate monitoring (e.g. ECGs) should be considered (see section "Warnings and precautions").

There are no available clinical data for the use of berotralstat in patients with end stage renal disease (ESRD) requiring haemodialysis. As a precautionary measure, it is preferable to avoid the use of berotralstat in patients with ESRD (see section "Pharmacokinetics").

Elderly patients

No dose adjustment is required for patients above 65 years of age (see sections "Warnings and precautions" and "Pharmacokinetics").

Children and adolescents

The safety and efficacy of berotralstat in children under 12 years of age have not yet been established. No data are available.

Delayed administration

If a dose of berotralstat is missed, the patient should take the forgotten dose as soon as possible without exceeding one dose per day.

Mode of administration

Orladeyo is for oral use. The capsule can be taken at any time of the day, with food (see section "Pharmacokinetics").

Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section "Composition").

Warnings and precautions

General

Orladeyo is not intended for treatment of acute HAE attacks, individualised treatment should be initiated with an approved rescue medicinal product.

There are no available clinical data on the use of berotralstat in HAE patients with normal C1 esterase inhibitor (C1-INH) activity.

There are no available data on the use of berotralstat in patients weighing less than 40 kg and use of berotralstat in these patients should be avoided.

QT prolongation

Patients with moderate or severe hepatic impairment may develop increased serum berotralstat concentrations that are associated with a risk of prolonged QT. Use of berotralstat in these patients should be avoided.

Patients with severe renal impairment may be at risk of prolonged QT. It is preferable to avoid the use of berotralstat in these patients. If treatment is required, appropriate monitoring (e.g. ECGs) should be considered.

There are no data available for the use of berotralstat in patients with independent risk factors for QT prolongation such as electrolyte disturbances, known pre-existing QT prolongation (either acquired or familial), advancing age (see section "Dosage/Administration"), or concomitant use of other medicinal products known to prolong the QT. It is preferable to avoid the use of berotralstat in these patients. If treatment is required, appropriate monitoring (e.g. ECGs) should be considered.

Women of childbearing potential

Berotralstat may reduce the effectiveness of oral hormonal contraceptives requiring CYP2C9 for conversion of prodrug to active metabolite, such as desogestrel. Therefore, women using only desogestrel for contraception should switch to an alternative method of effective contraception, such as barrier method, injectable progesterone, or combination oral hormonal contraception (see section "Interactions").

Interactions

Berotralstat is a P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrate.

Effect of Orladeyo on other medicinal products

CYP3A4 substrates

Berotralstat is a moderate inhibitor of CYP3A4, increasing the steady state maximum concentration (C_{max}) and AUC of oral midazolam by 45% and 124%, respectively, and the C_{max} and AUC of amlodipine by 45% and 77%, respectively. Concomitant administration may increase concentrations of other medicines that are CYP3A4 substrates. Refer to the product information for professionals for concomitant medicines that are predominantly metabolised by CYP3A4, particularly those with a narrow therapeutic index (e.g. cyclosporine, fentanyl). Dose adjustments of these medicines may be required (see section "Pharmacokinetics").

CYP2D6 substrates

Berotralstat is a moderate inhibitor of CYP2D6, increasing the C_{max} and AUC of dextromethorphan by 196% and 177%, respectively, and the C_{max} and AUC of desipramine by 64% and 87%, respectively.

Concomitant administration may increase exposure of other medicines that are CYP2D6 substrates. Refer to the product information for professionals for concomitant medicines that are predominantly metabolised by CYP2D6, particularly those with a narrow therapeutic index (e.g. thioridazine, pimozide) or whose prescribing information recommends therapeutic monitoring (e.g. tricyclic antidepressants). Dose adjustments of these medicines may be required (see section "Pharmacokinetics").

CYP2C9 substrates

Berotralstat is a weak inhibitor of CYP2C9 increasing the C_{max} and AUC of tolbutamide by 19% and 73%, respectively. No dose adjustment is recommended for concomitant use of medicines that are predominantly metabolised by CYP2C9 (e.g. tolbutamide) (see section "Pharmacokinetics").

CYP2C19 substrates

Berotralstat is not an inhibitor of CYP2C19, as C_{max} and AUC of omeprazole were increased by only 21% and 24%, respectively. No dose adjustment is recommended for concomitant use of medicines that are predominantly metabolised by CYP2C19 (e.g. omeprazole) (see section "Pharmacokinetics").

P-gp substrates

Berotralstat is a weak inhibitor of P-gp and increased the C_{max} and AUC of the P-gp substrate digoxin by 58% and 48%, respectively. Refer to the product information for professionals for concomitant medicines that are P-gp substrates, particularly those with a narrow therapeutic index (e.g. digoxin) or whose prescribing information recommends therapeutic monitoring (e.g. dabigatran). Dose adjustments of these medicines may be required (see section "Pharmacokinetics").

Oral contraceptives

Administration of berotralstat during use of oral contraceptives has not been studied. As a moderate inhibitor of CYP3A4, berotralstat may increase concentrations of oral contraceptives metabolised by CYP3A4. As a mild inhibitor of CYP2C9, berotralstat may reduce the effectiveness of hormonal contraceptives requiring CYP2C9 for conversion of prodrug to active metabolite, such as desogestrel. Therefore, women using only desogestrel for contraception should switch to an alternative method of effective contraception, such as barrier method, injectable progesterone, or combination oral hormonal contraception (see section "Warnings and precautions").

Effect of other medicinal products on Orladeyo

P-gp and BCRP inhibitors

Cyclosporine, a P-gp and BCRP inhibitor, increased the C_{max} of berotralstat by 25% and the AUC of berotralstat by 55%. Berotralstat exposure may be increased with concomitant administration of P-gp and BCRP inhibitors, but no dose adjustment is necessary. Close monitoring for adverse events is recommended for concomitant use with P-gp and BCRP inhibitors.

P-gp and BCRP inducers

Berotralstat is a substrate of P-gp and BCRP. P-gp and BCRP inducers (e.g. rifampicin, St. John's wort) may decrease berotralstat plasma concentration, leading to reduced efficacy of berotralstat. The use of P-gp inducers is not recommended with berotralstat.

Pregnancy, lactation

Women of childbearing potential

Women of childbearing potential must use effective contraception during treatment with berotralstat and for at least 1 month following the last dose. Berotralstat is not recommended in women of childbearing potential not using contraception (see section "Warnings and precautions").

Pregnancy

There are no or limited amount of data from the use of berotralstat in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section "Preclinical data").
Berotralstat is not recommended during pregnancy.

Lactation

Available pharmacodynamic/toxicological data in animals have shown excretion of berotralstat in milk (see section "Preclinical data").
A risk to the suckling child cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Orladeyo therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No effect on fertility was observed in animal studies (see section "Preclinical data").

Effects on ability to drive and use machines

Orladeyo has no or negligible influence on the ability to drive and use machines.

Undesirable effects

Summary of the safety profile

The most common adverse reactions are abdominal pain (all locations) (reported by 21% of patients), diarrhoea (reported by 15% of patients), and headache (reported by 13% of patients). The gastrointestinal events were reported primarily in the first 1-3 months of Orladeyo use (median day of onset was day 66 for abdominal pain and day 45 for diarrhoea) and resolved without medicinal product while Orladeyo treatment was continued. Almost all events (99%) of abdominal pain were mild or moderate with a median duration of 3.5 days (95% CI 2-8 days). Almost all events (98%) of diarrhoea were mild or moderate with a median duration of 3.2 days (95% CI 2-8 days).

List of adverse reactions

The safety of Orladeyo has been evaluated in long term clinical studies in patients with HAE (both uncontrolled, open-label and placebo-controlled, blinded) in 381 patients. Adverse reactions are listed below by MedDRA system organ class and by frequency. Frequencies are defined as follows: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions observed in clinical studies

System organ class	Frequency	Adverse reactions
Nervous system disorders	Very common	Headache[a]
Gastrointestinal disorders	Very common	Abdominal pain[b], Diarrhoea[c]
	Common	Vomiting, Gastroesophageal reflux, Flatulence
Skin and subcutaneous tissue disorders	Common	Rash
Investigations[d]	Common	ALT increased, AST increased

[a] Includes the events of Headache, Sinus headache

[b] Includes the events of Abdominal pain, Abdominal discomfort, Abdominal pain upper, Abdominal pain lower, Epigastric discomfort, Abdominal tenderness

[c] Includes the events of Diarrhoea, Faeces soft, Frequent bowel movements

[d] LFT elevations, which generally improved with or without discontinuation of berotralstat, were observed in some patients, primarily in those who discontinued androgen therapy within 14 days of initiating Orladeyo treatment. Abrupt discontinuation of androgens immediately prior to initiating Orladeyo should be avoided.

Paediatric population

The safety of Orladeyo was evaluated in clinical studies in a subgroup of 28 adolescent patients aged 12 to < 18 years of age and weighing at least 40 kg. The safety profile was similar to that observed in adults.

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 adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

No case of overdose has been reported in clinical studies. There is no available information to identify potential signs and symptoms of overdose. If symptoms should occur, symptomatic treatment is recommended. There is no antidote available.

Properties/Effects

ATC code

B06AC06
Pharmacotherapeutic group: Other haematological agents, drugs used in hereditary angioedema

Mechanism of action

Berotralstat is an inhibitor of plasma kallikrein. Plasma kallikrein is a serine protease that cleaves high-molecular-weight-kininogen (HMWK), releasing bradykinin, a potent vasodilator that increases vascular permeability. In patients with HAE due to C1-INH deficiency or dysfunction, normal regulation of plasma kallikrein activity is impaired, which leads to uncontrolled increases in plasma kallikrein activity and bradykinin release, resulting in HAE attacks consisting of swelling (angioedema).

Cardiac electrophysiology

At the steady state C_{max} of berotralstat at the recommended dose of 150 mg once daily, the mean corrected QT interval increased by 3.4 msec (90% upper CI bound of 6.8 msec), which is below the 10 msec threshold for concern. At a supratherapeutic dose of 450 mg once daily, steady state exposures were 4-fold higher than at the recommended 150 mg dose, and the corrected QT interval increased by a mean of 21.9 msec.

Pharmacodynamics

See section "Mechanism of action".

Clinical efficacy

Efficacy of berotralstat was studied in a multicentre, randomised, double-blind, placebo-controlled, parallel-group study NCT 03485911.

Study NCT 03485911

This study included 120 patients (114 adults and 6 children 12 years and over) with type I or II HAE who experienced at least two investigator-confirmed attacks within the first 8 weeks of the run-in period and took at least one dose of study treatment. Nine patients were aged ≥ 65 years. Patients were randomised into 1 of 3 parallel treatment arms, stratified by baseline attack rate, in a 1:1:1 ratio (berotralstat 110 mg, berotralstat 150 mg or placebo by oral administration once daily, with food) for the 24-week treatment period.

A total of 81 patients received at least one dose of berotralstat in the 24-week treatment period. Overall, 66% of patients were female and 93% of patients were Caucasian with a mean age of 41.6 years. A history of laryngeal angioedema attacks was reported in 74% of patients and 75% reported prior use of long-term prophylaxis. The median attack rate during the prospective run-in period (baseline attack rate) was 2.9 per month. Of patients enrolled, 70% had a baseline attack rate of ≥ 2 attacks per month.

Patients discontinued other prophylactic HAE medicinal products prior to entering the study; however, all patients were allowed to use rescue medicinal products for treatment of breakthrough HAE attacks. In berotralstat-treated patients, 51.4% of breakthrough attacks were treated with C1-INH (see section "Warnings and precautions"). Concomitant use of C1-INH and berotralstat did not result in any identifiable adverse reactions.

Orladeyo 150 mg produced a statistically significant and clinically meaningful reduction in the rate of HAE attacks compared to placebo through 24 weeks in the primary endpoint Intent-to-Treat (ITT) population as shown in Table 2. The percent reduction in HAE attack rate was greater with Orladeyo 150 mg compared to placebo, regardless of attack rate during the run-in period.

Table 2: Reduction in HAE attack rate in the berotralstat 150 mg ITT population

Outcome	**Berotralstat 150 mg** (n=40)			**Placebo** (n=40[a)]
	Rate per 28 days	**Percent reduction from placebo** (95% CI)	**p-value**	**Rate per 28 days**
HAE attack rate	1.31	44.2% (23.0, 59.5)	< 0.001	2.35

[a] One patient in the ITT analysis was randomised to placebo but was not treated.

Reduction in attack rates was sustained through 24 weeks.

Of patients receiving 150 mg berotralstat, 58% had a ≥ 50% reduction in their HAE attack rates compared to baseline versus 25% of placebo patients.

Paediatrics

The safety and effectiveness of Orladeyo were evaluated in 28 adolescent patients aged 12 to < 18 years across both studies. The safety profile and attack rate on study were similar to those observed in adults.
The safety and efficacy of berotralstat in paediatric patients under 12 years have not been established.

For Orladeyo the obligation to submit the results of studies in one or more subsets of the paediatric population in the treatment of hereditary angioedema for the prevention of attacks in patients with hereditary angioedema has been deferred (see section "Dosage/Administration" for information on paediatric use).

Pharmacokinetics

Absorption

Following oral administration of berotralstat 150 mg once daily, C_{max} and area under the curve over the dosing interval (AUC_{tau}) are 158 ng/mL (range: 110 to 234 ng/mL) and 2770 ng*h/mL (range: 1880 to 3790 ng*h/mL), respectively. The pharmacokinetics of berotralstat in patients with HAE are similar to those of healthy people.

Berotralstat exposure (C_{max} and AUC) increases greater than proportionally with dose and steady state is reached by days 6 to 12.

Food effect

No differences in the C_{max} and AUC of berotralstat were observed following administration with a high-fat meal. However the median t_{max} was delayed by 3 hours, from 2 hours (fasted) to 5 hours (fed, range: 1 to 8 hours). Berotralstat is to be administered with food to minimise gastrointestinal adverse events.

Distribution

Plasma protein binding is approximately 99%. After a single dose of radiolabelled berotralstat 300 mg, the blood to plasma ratio was approximately 0.92. At steady state, the geometric mean (%CV) Vd/F was 3123 L (40%) for berotralstat 150 mg once daily.

Metabolism

Berotralstat is metabolised by CYP2D6 and by CYP3A4 with low turnover *in vitro*. After a single oral radiolabelled berotralstat 300 mg dose, berotralstat represented 34% of the total plasma radioactivity, with 8 metabolites, each accounting for between 1.8 and 7.8% of the total radioactivity. Structures for

5 of the 8 metabolites are known. It is unknown whether any metabolites are pharmacologically active.

Berotralstat 150 mg once daily is a moderate inhibitor of CYP2D6 and CYP3A4, and a weak inhibitor of CYP2C9. Berotralstat is not an inhibitor of CYP2C19.
Berotralstat at double the recommended dose is a weak inhibitor of P-gp and is not an inhibitor of BCRP.

Elimination

After a single dose of 150 mg, the median half-life of berotralstat was approximately 93 hours (range: 39 to 152 hours).

After a single oral radiolabelled berotralstat 300 mg dose, approximately 9% was excreted in urine (3.4% unchanged; range 1.8 to 4.7%) and 79% was excreted in faeces. Additional analyses indicated approximately 50% of the fraction recovered in the faeces was unchanged berotralstat.

Kinetics in specific patient groups

Population pharmacokinetic analyses showed that age, gender and race did not meaningfully influence the pharmacokinetics of berotralstat. Body weight was identified as a covariate describing the variability of clearance and volume of distribution, resulting in higher exposure (AUC and C_{max}) in patients weighing less. However, this difference is not considered to be clinically relevant and no dose adjustments are recommended for any of these demographics.

Hepatic impairment

The pharmacokinetics of a single 150 mg oral dose of berotralstat were studied in patients with mild, moderate and severe hepatic dysfunction (Child-Pugh Class A, B or C). The pharmacokinetics of berotralstat were unchanged in patients with mild hepatic impairment compared to patients with normal hepatic function. In patients with moderate hepatic impairment, C_{max} was increased by 77%, while $AUC_{0\text{-}inf}$ was increased by 78%. In subjects with severe hepatic impairment, C_{max} was increased by 27%, while $AUC_{0\text{-}inf}$ was decreased by 6%. The estimated increase in mean QTcF in patients with moderate to severe hepatic dysfunction was up to 8.8 msec (2 sided 90% UB 13.1 msec). Use of berotralstat should be avoided in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C).

Renal impairment

The pharmacokinetics of a single 200 mg oral dose of berotralstat were studied in patients with severe renal impairment (eGFR less than 30 mL/min). When compared to a concurrent cohort with normal renal function (eGFR greater than 90 mL/min); C_{max} was increased by 39%, while no difference was observed in AUC. No dose adjustment is required for patients with mild or moderate

renal impairment. Patients with severe renal impairment may be at risk of prolonged QT. It is preferable to avoid the use of berotralstat in these patients.

The pharmacokinetics of berotralstat in patients with kidney failure requiring haemodialysis has not been studied. Given the high plasma protein binding of berotralstat, it is unlikely to be cleared by haemodialysis.

Elderly patients

Berotralstat has not been studied in patients above 75 years of age; however, age is not expected to affect exposure to berotralstat.

Children and adolescents

Based on population pharmacokinetic analyses that included paediatric patients 12 to < 18 years and weighing at least 40 kg, exposure at steady state following oral administration of berotralstat 150 mg once daily was slightly higher (29% higher) than adult exposure, with an estimated geometric mean (CV%) AUC_{tau} of 2515 (38.6) ng*h/mL. However, this difference is not considered to be clinically relevant, and no dose adjustments are recommended in paediatric patients 12 to < 18 years of age weighing 40 kg or more.

Preclinical data

Repeated dose toxicity

In non-clinical chronic repeat-dose toxicity studies, phospholipidosis (presence of foamy vacuolated macrophages) was observed in the liver of rats (by electron microscopy) and suspected in the liver, small intestine, lung, spleen and lymphoid tissue in rats and monkeys, at clinically relevant exposures. The clinical relevance of these findings is unknown.

Skeletal myofiber degeneration/necrosis was observed in the 2-year (lifetime) study in rats. Exposure at the no observed adverse effect level (NOAEL) for these findings in rats was 4.5 times the exposure achieved (on an AUC basis) at the clinical 150 mg berotralstat dose.

Genotoxicity

Non-clinical data reveal no special hazard for humans based on conventional studies of genotoxicity.

Carcinogenicity

There was no increase in tumours in a 6-month study in Tg rasH2 transgenic mice. Exposure in this mouse carcinogenicity study was 10 times the exposure achieved (on an AUC basis) at the clinical 150 mg berotralstat dose.

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.

Reproductive toxicity

Berotralstat crossed the placental barrier in rats and rabbits. An embryo-foetal development study conducted in pregnant rats administered berotralstat at exposures 9.7 times the exposure achieved (on an AUC basis) at the clinical 150 mg berotralstat dose revealed no evidence of harm to the developing foetus. A second embryo-foetal development study in a relevant non-rodent species was not conducted.
Berotralstat was detected in the plasma of rat pups on lactation day 14 at approximately 5% of the maternal plasma concentration.

Berotralstat had no effects on mating or fertility in male and female rats at a dose 2.9 times the clinical 150 mg berotralstat dose on a mg/m^2 basis.

Other information

Incompatibilities

Not applicable.

Shelf life

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

Special precautions for storage

Do not store above 30°C.
Keep out of the sight and reach of children.

Instructions for handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

68464 (Swissmedic)

Packs

Packs with 28 hard capsules. [B]

Marketing authorisation holder

BioCryst Schweiz GmbH, 6300 Zug

Date of revision of the text

May 2022