ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼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 adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Orladeyo 150 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 150 mg berotralstat (as dihydrochloride).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule)

Capsule (19.4 mm × 6.9 mm) with white opaque body imprinted with “150” and light blue opaque cap imprinted with “BCX”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

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

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

Orladeyo is not intended for treatment of acute HAE attacks (see section 4.4).

Special populations

Elderly population
No dose adjustment is required for patients above 65 years of age (see sections 4.4 and 5.2).

Renal impairment
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 4.4).

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 5.2).

Hepatic impairment
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 5.2).

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

Method of administration

Orladeyo is for oral use. The capsule can be taken at any time of the day, with food (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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

An increase in QT prolongation may be observed with higher concentrations of berotralstat (see section 5.1).

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 4.2), 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.

4.5 Interaction with other medicinal products and other forms of interaction

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

Effects of other medicinal products on berotralstat

P-gp and BCRP inhibitors
Cyclosporine, a P-gp and BCRP inhibitor, decreased the maximum concentration (C_{max}) of a single 150 mg dose of berotralstat by 7% and increased the AUC by 27%. No dose adjustment of berotralstat 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.

Effects of berotralstat on other medicinal products

CYP3A4 substrates
Berotralstat is a moderate inhibitor of CYP3A4, increasing the 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 SmPC 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 5.2).

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 SmPC 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 5.2).

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 5.2).

The effect of berotralstat on the CYP2C9 conversion of desogestrel to etonogestrel (active metabolite) was negligible. No dose adjustment is recommended for concomitant use of desogestrel.

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 5.2).

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 SmPC 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 5.2).

Oral contraceptives
As a moderate inhibitor of CYP3A4, berotralstat may increase concentrations of oral contraceptives metabolised by CYP3A4. The coadministration of berotralstat with desogestrel increased the AUC of etonogestrel (active metabolite) by 58%, C_{max} was not affected. The effect of berotralstat on the CYP2C9 conversion of desogestrel to etonogestrel was negligible. No dose adjustment is recommended for concomitant use of desogestrel.

4.6 Fertility, pregnancy and 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.

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 5.3).
Berotralstat is not recommended during pregnancy.

Breast-feeding

Available pharmacodynamic/toxicological data in animals have shown excretion of berotralstat in milk (see section 5.3).
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 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 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)**.**

Tabulated 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 obtained from clinical studies and post-marketing surveillance are listed below by MedDRA system organ class and by frequency. Frequencies are defined as follows: 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 (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 and post-marketing surveillance

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
	Not known	Nausea
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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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.

Clinical efficacy and safety

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 4.4). 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.

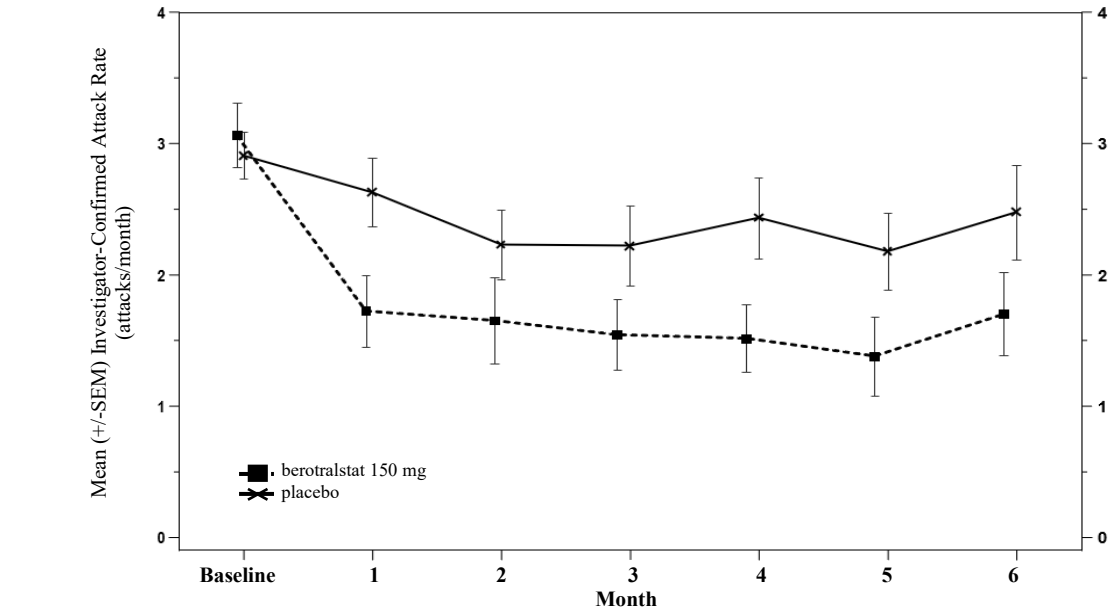
Table 2: Reduction in HAE attack rate in the berotralstat 150 mg ITT population

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, as shown in Figure 1.

Figure 1: HAE attack rate per month through 24 weeks treatment with berotralstat 150 mg (n=40) or placebo (n=40)



berotralstat 150 mg	N=	40	37	37	37	37	37	37
Placebo	N=	39	39	38	37	36	34	34

SEM: standard error of the mean

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

Orladeyo 150 mg reduced the rate of HAE attacks requiring treatment with standard of care acute attack treatments by 49.2% (95% CI: 25.5%, 65.4%) compared to placebo (rate per 28 days: 1.04 vs. 2.05).

Health-related quality of life
Patients receiving berotralstat 150 mg experienced an improvement in Angioedema Quality of Life Questionnaire (AE-QoL) total score and domain scores (functioning, fatigue/mood, fear/shame and nutrition) compared to the placebo group as shown in Table 3. A reduction of 6 points is considered a clinically meaningful improvement. The largest improvement was observed in the functioning score.

Table 3: Change in AE-QoL score*- berotralstat compared to placebo at week 24

	LS mean change (SE) from baseline at week 24		**LS mean difference from placebo (95% CI)**
	Berotralstat 150 mg	**Placebo**	
AE-QoL total score	-14.6 (2.6)	-9.7 (2.6)	-4.90 (-12.23, 2.43)
Functioning score	-19.5 (3.4)	-10.4 (3.4)	-9.10 (-18.58, 0.38)
Fatigue/Mood score	-11.3 (3.2)	-9.2 (3.3)	-2.16 (-11.35, 7.03)
Fear/Shame score	-15.4 (3.2)	-10.5 (3.3)	-4.96 (-14.05, 4.13)
Nutrition score	-8.8 (3.0)	-6.1 (3.1)	-2.68 (-11.27, 5.92)

AE-QoL=Angioedema Quality of Life Questionnaire; CI=confidence interval; LS=least squares; SE=standard error
*Lower scores indicate improved quality of life (lower impairment)

Paediatric population

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.

The European Medicines Agency has deferred the obligation to submit the results of studies with Orladeyo 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 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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.

Biotransformation

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.

Special populations

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.

Paediatric population
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.

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.

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).

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

5.3 Preclinical safety data

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.

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

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.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule filling

Crospovidone (type A)
Magnesium stearate
Silica, colloidal anhydrous
Starch, pregelatinised

Capsule shell

Gelatin
Titanium dioxide (E 171)
Indigo carmine (E 132)
Black iron oxide (E 172)
Red iron oxide (E 172)

Printing ink

Black iron oxide (E 172)
Potassium hydroxide
Shellac
Propylene glycol (E 1520)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PCTFE/PVC-Alu blisters in a carton with 7 capsules per blister

Pack size: 28 or 98 hard capsules

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

BioCryst Ireland Limited
Block 4, Harcourt Centre, Harcourt Road, DUBLIN 2, D02HW77
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1544/001
EU/1/21/1544/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 April 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Millmount Healthcare Limited
Block-7, City North Business Campus
Stamullen,
Co. Meath, K32 YD60
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Orladeyo 150 mg hard capsules
berotralstat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 150 mg berotralstat (as dihydrochloride).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

hard capsule
28 hard capsules
98 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioCryst Ireland Limited
Block 4, Harcourt Centre, Harcourt Road, DUBLIN 2, D02HW77
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1544/001
EU/1/21/1544/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Orladeyo

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Orladeyo 150 mg capsules
berotralstat

2. NAME OF THE MARKETING AUTHORISATION HOLDER

BioCryst Ireland Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Orladeyo 150 mg hard capsules
berotralstat

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Orladeyo is and what it is used for

Orladeyo is a medicine that contains the active substance berotralstat. It is used to **prevent angioedema attacks** in adults, and adolescents aged from 12 years with hereditary angioedema.

What hereditary angioedema is

Hereditary angioedema is a condition that often runs in families. It can limit your daily activity by causing attacks of swelling and pain in different parts of your body including:
- hands and feet
- face, eyelids, lips or tongue
- voice-box (larynx), which may make breathing difficult
- genitals
- stomach and intestines

How Orladeyo works

In hereditary angioedema your blood does not have enough of a protein called C1 inhibitor, or the protein does not work properly. This leads to too much of the enzyme plasma kallikrein, which in turn increases the levels of bradykinin in your bloodstream. Too much bradykinin leads to symptoms of hereditary angioedema. Berotralstat, the active substance in Orladeyo, blocks the activity of plasma kallikrein and so reduces bradykinin. This prevents the swelling and pain that hereditary angioedema can cause.

2. What you need to know before you take Orladeyo

Do not take Orladeyo

- if you are allergic to berotralstat or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your doctor or pharmacist before taking Orladeyo if you:
- have moderate or severely reduced liver function which can increase blood levels of berotralstat
- have severely reduced kidney function
- are at risk for a certain heartbeat abnormality, known as QT prolongation

Treat a hereditary angioedema attack with your regular rescue medicine without taking additional doses of Orladeyo. It is not known if Orladeyo works for immediate treatment of attacks of hereditary angioedema.

Children and adolescents

Orladeyo is not recommended in children under 12 years. This is because it has not been studied in this age group.
Orladeyo has not been studied in adolescents weighing less than 40 kg.

Other medicines and Orladeyo

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Particularly, tell your doctor before taking Orladeyo if you are using:
- thioridazine or pimozide, medicines to treat mental disorders
- amlodipine, a medicine to treat high blood pressure or a type of chest pain called angina
- ciclosporin, a medicine to suppress the immune system, treat severe skin diseases and severe eye or joint inflammation
- dabigatran, a medicine to prevent blood clotting
- rifampicin: a medicine to treat tuberculosis or certain other infections
- desipramine, St. John’s wort and other medicines to treat depression called tricyclic antidepressants
- dextromethorphan, a cough-relieving medicine
- digoxin, a medicine to treat heart problems and irregular heartbeat
- fentanyl, a strong painkiller
- midazolam, a medicine to treat sleeping disorders and for anaesthesia
- tolbutamide, a medicine to reduce blood sugar
- oral contraceptives, medicines used for birth control

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

There is limited information on the use of Orladeyo during pregnancy and breast-feeding. As a precaution, it is preferable to avoid the use of Orladeyo during pregnancy and breast-feeding. Your doctor will discuss with you the risks and benefits of taking this medicine.

Women of childbearing potential must use effective contraception during treatment and for at least 1 month following the last dose. Orladeyo is not recommended in women of childbearing potential not using contraception.

Driving and using machines

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

3. How to take Orladeyo

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose for adults and adolescents from 12 years weighing ≥ 40 kg is one capsule once daily.

Orladeyo is not recommended in patients with moderate or severely reduced liver function.

If your kidney function is severely reduced, treatment with Orladeyo should be avoided. However, if your doctor considers that treatment with Orladeyo is needed, then additional monitoring, including monitoring of your heart rhythm with tests such as an electrocardiogram (ECG, a test of the heart's electrical activity), may be required. If you are on dialysis due to kidney disease, treatment with Orladeyo should be avoided.

Method of administration

Take the capsule with food and one glass of water at the same time each day. This can be at any time of the day.

If you take more Orladeyo than you should

Contact your doctor immediately if this occurs.

If you forget to take Orladeyo

Do not take a double dose to make up for a forgotten capsule. Take a missed dose as soon as you remember; however, do not take more than one dose per day.

If you stop taking Orladeyo

It is important to **take** this medicine on a regular basis and for **as long as your doctor prescribes it**. Do not stop taking it without approval from your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects can occur with the following frequencies:
Very common, may affect more than 1 in 10 people
- headache
- stomach pain, including abdominal (belly) discomfort, abdominal tenderness
- diarrhoea and frequent bowel movements

Common, may affect up to 1 in 10 people
- vomiting
- heartburn
- wind
- blood tests showing increased levels of liver enzymes called ALT and AST
- rash

Not known, frequency cannot be estimated from the available data
- nausea (feeling sick)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Orladeyo

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Orladeyo contains

- The active substance is berotralstat. Each capsule contains 150 mg berotralstat (as dihydrochloride).
- The other ingredients are:
  - starch, pregelatinised, crospovidone (type A), silica, colloidal anhydrous, magnesium stearate, gelatin, titanium dioxide (E 171)
  - colourants: indigo carmine (E 132), black iron oxide (E 172), red iron oxide (E 172)
  - edible printing ink: black iron oxide (E 172), potassium hydroxide, shellac, propylene glycol (E 1520)

What Orladeyo looks like and contents of the pack

Orladeyo capsules have a white opaque body imprinted with “150” and light blue opaque cap imprinted with “BCX” (19.4 mm × 6.9 mm). They are packed in plastic/aluminium blisters in a carton with 7 capsules per blister.

Pack size: 28 or 98 hard capsules

Marketing Authorisation Holder and Manufacturer

- **Marketing Authorisation Holder**
  BioCryst Ireland Limited
  Block 4, Harcourt Centre, Harcourt Road, DUBLIN 2, D02HW77
  Ireland

- **Manufacturer**
  Millmount Healthcare Limited
  Block-7, City North Business Campus,
  Stamullen,
  Co. Meath, K32 YD60
  Ireland

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
https://www.ema.europa.eu

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for berotralstat, the scientific conclusions of PRAC are as follows:

In view of available data on nausea from spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and/or re-challenge and in view of a plausible mechanism of action, the PRAC considers that a causal relationship between berotralstat and nausea is at least a reasonable possibility. The PRAC concluded that the product information of products containing berotralstat should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation

On the basis of the scientific conclusions for berotralstat the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing berotralstat is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation should be varied.