Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed medicines and medicines used outside their licence, to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life-threatening conditions where there are no adequate treatment options. More information about the scheme can be found here: http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the EAMS medicine. This medicine does not yet have a licence (marketing authorisation) and the information is provided to assist physicians in prescribing this unlicensed medicine. Guidance on prescribing unlicensed medicines can be found on the GMC webpage:
https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

The scientific opinion is based on assessment of the information supplied to the MHRA on the benefits and risks of this promising new medicine. As such, this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to license such a medicine, nor should it be regarded as an authorisation to sell or supply such a medicine. A positive scientific opinion is not a recommendation for use of the medicine and should not be interpreted as such. Under EAMS the risk and legal responsibility for prescribing a 'special' remains with the physician, and the opinion and EAMs documentation published by the MHRA are intended only to inform physicians' decision making and not to recommend use. An EAMS scientific opinion does not affect the civil liability of the manufacturer or any physician in relation to the product.

Healthcare professionals should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Scientific opinion period: The MHRA will withdraw the EAMS positive scientific opinion when a marketing authorisation (drug licence) is issued for the EAMS product covering the EAMS indication, or if following scientific assessment, the EAMS criteria are considered to be no longer met.

Treatment protocol update(s): In case of substantial new efficacy or safety data, the treatment protocol may need to be updated.

Contact information regarding queries on using this EAMS medicine can be found at the end of this document.

Information for the healthcare professionals

1. NAME OF THE MEDICINAL PRODUCT

Berotralstat 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 EAMS therapeutic indication

Berotralstat 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

Treatment must be initiated and supervised by a Physician

Posology

The recommended dose for adults and adolescents from 12 years is 150 mg berotralstat once daily.

Inform the patient that it is important to not miss or skip doses. It is recommended that the patient takes a missed dose as soon as the patient remembers; however, do not take more than one dose within one day.

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

Method of administration

Berotralstat is for oral use. The capsule should be taken with one glass of water at the same time each day. This can be at any time of the day, with or without 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

Berotralstat is not intended for treatment of acute HAE attacks, individualised treatment should be initiated with an approved rescue medication.

As there are no available clinical data on the use of berotralstat in HAE patients with normal C1-INH activity, treatment with berotralstat is not recommended.

There are no available data on the use of berotralstat in adolescent patients weighing less than 40 kg.

QTc interval

Patients with moderate to severe hepatic impairment (Childs-Pugh class B or C) may develop increased berotralstat drug levels that are associated with a risk of prolonged QTc. Berotralstat should be used with caution in these patients, as well as in those whose body weight is <40Kg or if there are additional independent risk factors for QTc prolongation such as electrolyte disturbances, known preexisting QTc prolongation (either acquired or familial) or concomitant use of other drugs known to either prolong the QTc (e.g. ondansetron) or increase berotralstat drug levels (cyclosporine).

Women of childbearing potential

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 4.5).

Special populations

Elderly population

Age did not affect exposure to berotralstat. No dose adjustment is required for patients above 65 years of age (see section 5.2).

Consider potential for drug interaction in patients taking multi-drug therapy for other conditions (see section 4.5).

Renal impairment

No dose adjustment is required for patients with mild, moderate or severe renal impairment who are not on dialysis. 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, moderate or severe hepatic impairment. Berotralstat should be used with caution in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) and appropriate clinical monitoring is recommended. See section 5.2.

Paediatric population

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

4.5 Interaction with other medicinal products and other forms of interaction

Berotralstat is a P-gp and BCRP substrate.

Effects of other medicinal products on berotralstat

P-gp and BCRP inhibitors
Cyclosporine, a P-gp and BCRP inhibitor, increased the steady state maximum concentration (C_{max}) of berotralstat by 25% and the AUC of berotralstat by 55% (see section 5.2).

Berotralstat exposure may be increased with concomitant administration of P-gp and BCRP inhibitors, but no dose adjustment is necessary.

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% to 124%, respectively, and the C_{max} and AUC of amlodipine by 45% to 77%, respectively. Concomitant administration may increase concentrations of other medicines that are CYP3A4 substrates. Appropriate clinical monitoring is recommended for concomitant medicines that are predominantly metabolised by CYP3A4, particularly those with a narrow therapeutic index (e.g. cyclosporine, fentanyl), and 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. Appropriate clinical monitoring is recommended 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), and 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.

CYP2C19 substrates
Berotralstat is not an inhibitor of CYP2C19, as C_{max} and AUC 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. Appropriate clinical monitoring is recommended 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), and dose adjustments of these medicines may be required. (see section 5.2).

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 must switch to an alternative method of effective contraception, such as barrier method, injectable progesterone, or combination oral hormonal contraception (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of berotralstat in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of berotralstat during pregnancy.

Breast-feeding

There are no data on the presence of berotralstat in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of berotralstat in milk (see section 5.3). A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from berotralstat 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

Berotralstat 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) (21%) and diarrhoea (15%). These events most often occur early after initiation of treatment and become less frequent with continued berotralstat use. Most of these events were brief in duration and resolved without medication while berotralstat treatment was continued.

Tabulated summary of adverse reactions

The safety of berotralstat has been evaluated in clinical studies in patients with HAE (both uncontrolled, open-label and placebo-controlled, blinded) in over 325 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 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).

Table 1: Adverse reactions observed in clinical studies

System Organ Class	Frequency	Adverse Reactions
Gastrointestinal disorders	Very common	Abdominal pain [a], diarrhoea [b],
	Common	Vomiting, Gastroesophageal reflux, flatulence
Skin and subcutaneous tissue disorders	Common	Rash
Investigations	Common	ALT increased, AST increased

[a] Includes events of Abdominal pain, Abdominal discomfort, Abdominal pain upper, Abdominal pain lower, Epigastric discomfort, Abdominal tenderness
[b] Includes the events of Diarrhoea, Faeces soft, Frequent bowel movements

Paediatric population

The safety of berotralstat was evaluated in clinical trials 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 Yellow Card and to BioCryst by completing the AE form provided in the physician pack.

4.9 Overdose

No case of overdose has been reported in clinical trials. 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: not yet assigned ATC code: not yet assigned

Mechanism of action

Berotralstat is an orally administered 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 hereditary angioedema (HAE) due to C1-inhibitor (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), pain, and limitation of function. Berotralstat decreases plasma kallikrein activity to control excess bradykinin generation in patients with HAE.

Pharmacodynamic effects

Concentration-dependent inhibition of plasma kallikrein, measured as a reduction from baseline of specific enzyme activity, was demonstrated after oral administration of berotralstat once daily in patients with HAE.

Cardiac electrophysiology

At the steady state C_{max} of berotralstat at the recommended dose of 150 mg, 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 regulatory concern. At a supratherapeutic steady state dose of 450 mg, exposures were 4-fold higher than achieved 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 the multicentre, randomised, double-blind, placebo-controlled, parallel-group study NCT 03485911. The safety was also investigated in this study and in the open-label, non-randomised study NCT 03472040.

Study NCT 03485911

The efficacy study included 120 adults and 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 (Part 1).

Eligible patients were able to continue active treatment with berotralstat, blinded to dose, in Part 2 through 48 weeks. Patients on placebo in Part 1 were subsequently randomised in Part 2 to active treatment at either 110 or 150 mg. All patients could subsequently rollover to open-label treatment with berotralstat 150 mg in Part 3.

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.

A total of 81 patients received at least one dose of berotralstat in Part 1. Overall, 66% of patients were female and 93% of patients were Caucasian with a mean age of 41.6 years. The proportion of patients who discontinued berotralstat prematurely due to adverse events was 7% and 3% for patients treated with 110 mg or 150 mg, respectively, and 3% for placebo-treated patients. No deaths occurred in the trial.

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.

Berotralstat 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 berotralstat 150 mg compared to placebo, regardless of attack rate during the run-in period.

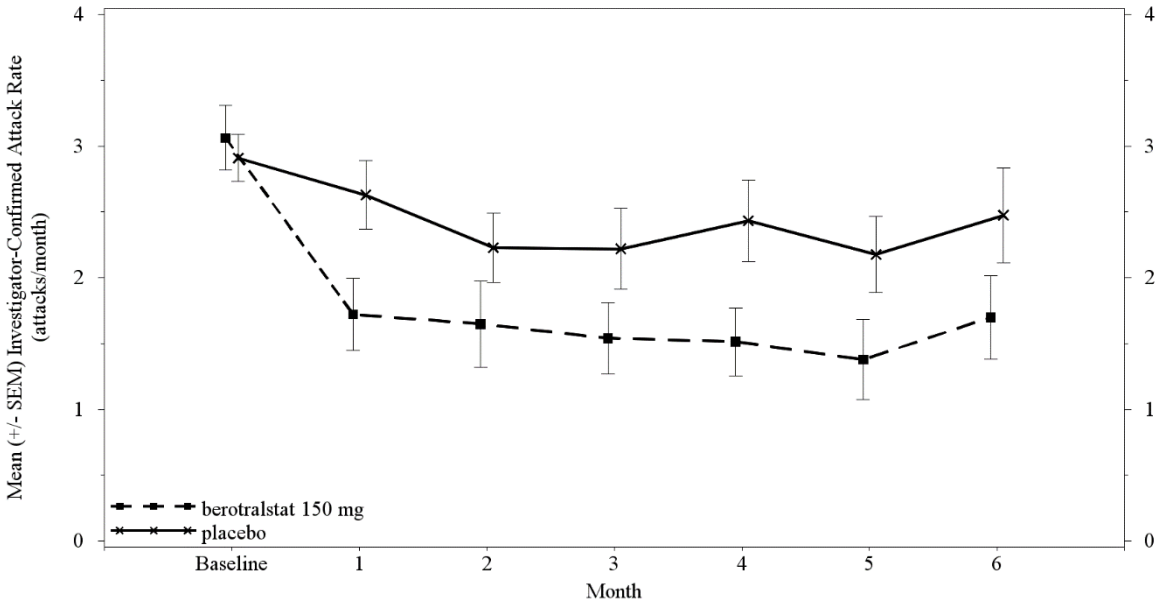
Table 2: Reduction in HAE attack rate in the berotralstat 150 mg ITT population

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

* One patient in the ITT analysis was randomised to placebo but was not treated.

Reduction in attack rates was observed in the first month of treatment with berotralstat 150 mg and 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)



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. In post-hoc analyses, 50% and 23% of patients receiving berotralstat 150 mg had a ≥ 70% or ≥ 90% reduction in their HAE attack rates compared to baseline versus 15% or 8% of placebo patients.

Study NCT 03472040

Berotralstat was studied in the open-label, non-randomised safety study in 266 patients aged 12 years and older who received 110 mg or 150 mg orally once daily, with food. In 89 patients who received berotralstat 150 mg and completed 48 weeks of dosing, the interim analysis indicates that the attack rates were consistent with the controlled study and sustained up to one year with treatment respectively.

Elderly

The safety and efficacy of berotralstat were evaluated in a subgroup of 9 patients aged ≥ 65 years in study NCT3485911. Results of the subgroup analysis by age were consistent with overall study results. The safety profile from an additional 5 patients aged ≥ 65 years enrolled in the open-label, long-term safety study (NCT 03472040) was consistent with data from the randomised, double-blind study.

Paediatric population

The safety and effectiveness of berotralstat were evaluated in 28 paediatric 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.

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 reached by days 6 to 12.

The median time to maximum plasma concentration (t_{max}) of berotralstat when administered with food is 5 hours (range: 1 to 8 hours).

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).

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.

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.

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.

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 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.

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/1.73 m^2). When compared to a concurrent cohort with normal renal function (eGFR greater than 90 mL/min/1.73 m^2), no clinically relevant differences were observed; C_{max} was increased by 39%, while no difference was observed in AUC. No dose adjustment is required for patients with mild, moderate or severe renal impairment.

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 function (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 or severe hepatic impairment, Cmax was increased by 50%, while AUC was increased by 38%. The estimated increase in mean QTcF at this exposure of berotralstat is 7.0 msec (2 sided 90% UB 10.9 msec). Berotralstat should be used with caution in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) and appropriate clinical monitoring is recommended.

5.3 Preclinical safety data

Carcinogenesis

There was no increase in tumours in a 6-month study in Tg rasH2 transgenic mice, when berotralstat was given by daily oral gavage at doses up to 50 mg/kg, which resulted in 10 times the exposure at the human 150 mg berotralstat dose on an AUC basis.
In a 2-year study in rats, berotralstat was given by daily oral gavage at doses of 3, 8 and 20 mg/kg. There was no increase in tumours in rats at 20 mg/kg/day, which resulted in 4.5 times the exposure at the human 150 mg berotralstat dose on an AUC basis.

Mutagenesis

Berotralstat was not mutagenic in laboratory assays.

Pregnancy

There are insufficient data available to inform about berotralstat-related risks with use in pregnancy. Berotralstat crossed the placental barrier in rats and rabbits. Embryo-foetal development studies conducted in pregnant rats and rabbits at doses resulting in exposures of 9.7 and 1.7 times the exposure achieved (on an AUC basis) at the human 150 mg berotralstat dose, respectively, revealed no evidence of harm to the developing foetus.

Breast-feeding

There are no data on the presence of berotralstat in human milk, its effects on the breast-fed infant or on milk production. Berotralstat was detected in the plasma of rat pups on lactation day 14 at approximately 5% of the maternal plasma concentration.

Fertility

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule filling

pregelatinised starch,
crospovidone,
colloidal silicon dioxide,
magnesium stearate

Capsule shell

gelatine,
titanium dioxide,
colorants (Indigo Carmine E132, black iron oxide E172, red iron oxide E172),
edible printing ink (black iron oxide E172, potassium hydroxide, shellac, propylene glycol)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

White plastic bottle

Pack size: 30 capsules, hard

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. SCIENTIFIC OPINION HOLDER

BioCryst UK Limited,
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United Kingdom,
TW9 1PL

8. EAMS NUMBER

32080/0001

9. DATE OF SCIENTIFIC OPINION

30th October 2020

Additional information

Prescribing physician will be provided with a primary physician pack containing all the relevant documents needed to manage patients receiving berotralstat under EAMS. This can be requested by sending an email to access@inceptua.com. Inceptua will provide the login to the physician in order to register at the EAMS portal. Upon registration, the prescribing physician will be required to complete the initial application and drug supply request form to confirm eligibility within the scheme once the patient has signed the informed consent form.

If the patient is considered eligible for EAMS, prescribing physicians will be provided with training and guidance documents on the safety reporting requirements and processes. The training must be completed before berotralstat supply and patient treatment

Contact information: medinfo@BIOCRYST.com

AE reporting: clinicalsafety@propharmagroup.com