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Berotralstat: A Review of Hereditary Angioedema

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Abstract

Berotralstat or ORLADEYO (BCX7353) is a highly selective oral kallikrein inhibitor that was recently approved for the prevention of angioedema attacks in adults and children aged 12 and older with hereditary angioedema. Hereditary angioedema is a rare genetic disorder characterized by recurrent episodes of severe swelling of the limbs, face, intestinal tract, and airway caused by a lack of a C1 esterase inhibitor (C1-INH). Because laryngeal edema can be fatal due to asphyxiation, proper diagnosis and management of hereditary angioedema are critical. Self-administration of treatment is advised and has been linked to improved quality of life in patients with hereditary angioedema. There is a significant unmet need for HAE treatment options that are less invasive than the currently available targeted parenteral prophylactic therapies. This need could be met with an oral medication that is both effective and well tolerated, with a lower adverse effect profile than the current oral agents. The efficacy and safety of berotralstat were evaluated in a single, well-controlled, adequately designed pivotal trial in Type I and II HAE patients 12 years of age and older. ORLADEYO is available in hard gelatin capsules of 150 mg (equivalent to 169.4 mg berotralstat dihydrochloride) and 110 mg (equivalent to 124.2 mg berotralstat dihydrochloride) for oral administration.

Keywords

Berotralstat, hereditary angioedema, Oral dosage form, Orladeyo.

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INTRODUCTION:

Hereditary angioedema is a rare genetic disorder characterized by recurrent episodes of severe swelling of the limbs, face, intestinal tract, and airway caused by a lack of C1 esterase inhibitor (C1-INH). Because laryngeal oedema can be fatal due to asphyxiation, proper diagnosis and management of hereditary angioedema is critical. Attacks of hereditary angioedema are mediated by bradykinin, the production of which is controlled by C1-INH. Hereditary angioedema treatment focuses on acute attacks as well as short and long-term prophylaxis. C1-INH concentrate, icatibant and ecallantide are examples of acute treatment options. Self-administration of treatment is advised and has been linked to improved quality of life in patients with hereditary angioedema. The outcomes and quality of life of patients with hereditary angioedema have improved as a result of advances in diagnosis and management. [1,2,3] The exact incidence and

prevalence of hereditary angioedema are unknown, but it is estimated that 1 in 50000 people worldwide suffer from it. [4] The median time from onset of symptoms to diagnosis is 1.4-8.5 years. [5] Delays in diagnosis are especially concerning because undiagnosed patients are at a higher risk of asphyxiation due to laryngeal oedema [6], because patients and physicians may be unaware of the potentially fatal nature of hereditary angioedema attacks and the appropriate treatment. Recent treatment guidelines recommend that prophylactic therapy be tailored to the patient's specific needs, taking into account factors such as attack frequency, lifestyle, and personal preferences. [7] Until recently, all available targeted prophylactic therapies were administered via intravenous or subcutaneous injection, imposing a significant treatment burden on patients and caregivers such as needle phobia and self-administration. [8,9] As a result, there is a significant unmet need for HAE treatment options that are less invasive than the currently available targeted parenteral prophylactic therapies. This need could be met with an oral medication that is both effective and well tolerated, with a lower adverse effect profile than the current oral agents. Berotralstat or ORLADEYO (BCX7353) is a highly selective oral kallikrein inhibitor that was recently approved for the prevention of angioedema attacks in adults and children aged 12 and older with HAE. [10] Berotralstat is available as a dihydrochloride salt under the chemical name 1-[3-(aminomethyl) phenyl]-N-(5-{(R)-(3-cyanophenyl) [(cyclopropylmethyl) amino]methyl} -2-fluorophenyl) -3-(trifluoromethyl) -1H-pyrazole -5- carboxamide dihydrochloride. Berotralstat dihydrochloride is a white to off-white powder that dissolves in water at pH ≤ 4. $C_{30}H_{26}F_4N_6O \cdot 2HCl$ is the molecular formula, and the molecular weight is 635.49. (dihydrochloride). ORLADEYO is available in hard gelatin capsules of 150 mg (equivalent to 169.4 mg berotralstat dihydrochloride) and 110 mg (equivalent to 124.2 mg berotralstat dihydrochloride) for oral administration. The structure of berotralstat hydrochloride shown in Fig.1. Each capsule contains berotralstat dihydrochloride as the active ingredient and the inactive ingredients colloidal silicon dioxide, crospovidone, magnesium stearate and pregelatinized starch. Berotralstat was designated as a SAKIGAKE product (SAKIGAKE Drug Designation No. 4 of 2015 [*27 yaku*]) as of October 27, 2015 and as an orphan drug (Orphan Drug Designation No. 425 of 2018 [*30 yaku*]) as of December 27, 2018, with the intended indication of "the suppression of attacks of hereditary angioedema."

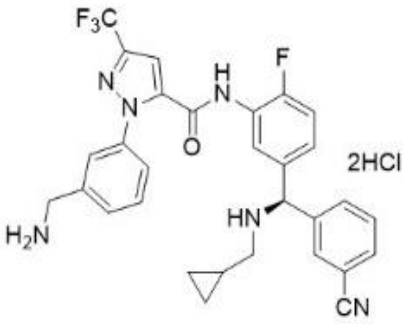

Fig 1: Structure of berotralstat hydrochloride

Risk assesment of berotralstat:

The efficacy and safety of berotralstat was evaluated in a single, well-controlled, adequately designed pivotal trial in Type I and II HAE patients 12 years of age and older. Patients had a minimum of 2 HAE attacks over a 2-month run-in period. Berotralstat treatment for 24 weeks versus placebo resulted in statistically significant and clinically meaningful reductions in the rate of HAE attacks. The 110 and 150 mg doses of berotralstat reduced the rate of HAE attacks by 30% ($p=0.024$) and 44% ($p<0.001$) relative to placebo, respectively. Efficacy was further supported by additional endpoints such as proportion of patients with at least a 50% reduction in HAE attacks compared to baseline. While the study demonstrated a significant treatment benefit in a patient population with frequent attacks who are likely to require prophylaxis, the treatment response was modest as few subjects achieved complete elimination of attacks. However, an oral therapy provides an additional, convenient option to the treatment armamentarium. [11]

Non-clinical pharmacokinetics:

The data on absorption, distribution, metabolism, excretion, and drug-drug interactions, in the form of the results from oral and intravenous administration studies in mice, rats, rabbits, and monkeys. Berotralstat or 2 types of 14C-berotralstat (A or B)4) were used in the pharmacokinetic studies. Plasma berotralstat concentrations were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (lower limit of quantification, 1 ng/mL in mouse and rabbit plasma, 1 or 5 ng/mL in rat plasma, 5 ng/mL in monkey plasma), and radioactivity concentrations in samples were determined using liquid scintillation counter or quantitative autoradiography. Unless otherwise specified, pharmacokinetic parameters are expressed as the mean or the mean ± standard deviation (SD), and doses are expressed as free base. [12]

Absorption:

1. Single-dose studies:

The pharmacokinetic parameters following a single oral or intravenous dose of berotralstat in rats or monkeys under fasting conditions. The absolute oral bioavailability of berotralstat was 33% in rats and 45% in monkeys.

2. Repeated-dose studies:

Berotralstat exposure increased in an approximately dose-proportional manner in mice and monkeys, and was supra proportional to dose in rats. While berotralstat exposure tended to be higher in female mice than in male mice, there were no consistent sex differences in rats and monkeys. No evident bioaccumulation of berotralstat occurred in mice, but berotralstat tended to accumulate in rats and at higher dose levels (≥55 mg/kg) in monkeys.

Distribution:

1. Tissue distribution:

Following a single oral dose of 14C-berotralstat A 30 mg/kg to albino and pigmented rats (1 male/time point), tissue distribution of radioactivity was determined by quantitative autoradiography. Radioactivity level peaked at 8 hours post-dose in many tissues. High radioactivity was detected at 8 hours post-dose in the liver, renal medulla, spleen, adrenal gland, kidney, lung, pituitary gland, and renal cortex in albino rats, and in the liver, spleen, adrenal gland, renal medulla, lung, renal cortex, pituitary gland, and kidney in pigmented rats (in descending order). In pigmented rats, radioactivity was eliminated from most tissues by 1,440 hours post-dose, and residual radioactivity was highest in the uvea. Since the radioactivity level in the uvea peaked at 72 hours post-dose and then declined over time, berotralstat was considered to reversibly bind to melanin. A phototoxicity study also showed that berotralstat has little phototoxic potential.

2. Plasma protein binding:

Berotralstat 3 µmol/L was added to the plasma from mouse, rat, rabbit,7) monkey,7) and human, and the plasma protein binding of berotralstat was determined using an equilibrium dialysis method. The plasma protein binding of berotralstat was 99.4 ± 0.03%, 98.9 ± 0.01%, 81.9 ± 0.37%, 74.1 ± 0.87%, and 98.7 ± 0.06%, respectively.

3. Distribution in blood cells:

When berotralstat 3 µmol/L was added to the whole blood from mouse, rat, rabbit) monkey) and human, the red blood cell to plasma ratios were 0.40, 1.08, 1.34, 0.33, and 1.74, respectively.

4. Placental transfer:

Pregnant rats (8/group) were dosed with oral berotralstat 10, 25, or 75 mg/kg/day from gestation days 6 to 17, and maternal and fetal plasma concentrations of berotralstat were determined. Maternal Cmax values on gestation day 17 in the berotralstat 10, 25, and 75 mg/kg/day groups were 191, 653, and 1,440 ng/mL, respectively. Fetal plasma concentrations of berotralstat at 4 hours after a maternal dose on gestation day 17 were 7.22, 46.3, and 73.7 ng/mL, respectively.

Pregnant rabbits (3/group) were dosed with oral berotralstat 20, 50, or 100 mg/kg/day from gestation days 7 to 20, and maternal and fetal plasma concentrations of berotralstat were determined. Maternal Cmax values on gestation day 19 in the berotralstat 20, 50, and 100 mg/kg/day groups were 83.3, 266, and 367 ng/mL, respectively. Fetal plasma concentrations of berotralstat at 3 hours after a maternal dose on gestation day 20 were 5.81, 30.4, and 40.7 ng/mL, respectively.

Metabolism:

1. *In-vitro* studies:

Recombinant human CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4) were incubated with berotralstat (2.7 µmol/L) for 1 hour in the presence or absence of nicotinamide adenine dinucleotide phosphate-oxidase (NADPH). Incubation with CYP2D6 and CYP3A4 in the presence of NADPH resulted in 15.0% and 22.4% loss of berotralstat, respectively. Incubation with other CYP isoforms in the presence of NADPH or with CYP2D6 and CYP3A4 in the absence of NADPH resulted in <10% loss of berotralstat. These results suggested that berotralstat is predominantly metabolized by CYP2D6 and CYP3A4.

Recombinant human CYP isoforms (CYP2D6 and CYP3A4) were incubated with berotralstat (10 µmol/L). Unchanged berotralstat and 9 different

metabolites including M3, M7, and M9 were detected.

Excretion:

1. Urinary, fecal excretion and billiary excretion:

Following the oral administration of 14C-berotralstat A 30 mg/kg in albino rats (3 males), the mean total recovery of radioactivity up to 168 hours post-dose was 99.8%, and urinary and fecal recoveries of radioactivity were 2.47% and 94.0%, respectively. The predominant components in these samples (the percentage of total radioactivity administered) were M3 (1.35%) and unchanged berotralstat (0.531%) in the urine up to 72 hours post-dose and unchanged berotralstat (20.7%), M7 (6.59%), M5 (4.89%), and M3 (4.55%) in the feces up to 120 hours post-dose.

2. Excretion into milk:

Lactating rats (4/group) were dosed with oral berotralstat 10, 25, or 45 mg/kg/day from gestation day 6 to lactation day 14. The mean plasma berotralstat concentrations in pups on lactation day 14 at 10, 25, and 45 mg/kg/day of berotralstat were 1.11, 8.53, and 29.5 ng/mL, respectively, in male pups and 1.50, 9.98, and 30.0 ng/mL, respectively, in female pups, suggesting berotralstat excretion into milk. The plasma berotralstat concentrations in dams at 4 hours post-dose on lactation day 14 were 63.8, 360.3, and 688.3 ng/mL, respectively

Primary pharmacodynamics:

The inhibition effect of berotralstat on human pKal was evaluated using a chromogenic substrate assay. The half maximal inhibitory concentration (IC50) was 0.88 nmol/L, and the inhibition constant (*Ki*) was 0.44 nmol/L. Using human umbilical vein endothelial cells (HUVEC) coated with high-molecular-weight kininogen, the inhibitory effect of berotralstat against bradykinin generation through pKal-mediated cleavage of high-molecular-weight kininogen was evaluated. Bradykinin levels in the supernatant were determined by an enzyme-linked immunosorbent assay (ELISA). Berotralstat decreased the bradykinin level concentration-dependently with a half-maximal effective concentration (EC50) of 5.56 nmol/L. The inhibitory effect of berotralstat against pKal activity in healthy subjects and patients with HAE was evaluated using a fluorogenic assay. The EC50 values of berotralstat for pKal activity in healthy subjects and patients with HAE were 5.4 nmol/L and 15.9 nmol/L, respectively. [13]

Secondary pharmacodynamics:

Because pKal is an upstream trigger for the intrinsic coagulation pathway, the effect of berotralstat on the blood coagulation system was evaluated using human plasma. Berotralstat prolonged the prothrombin time (PT) and the activated partial thromboplastin time (APTT) concentration-dependently, and the berotralstat concentrations required to produce a doubling of PT and APTT in human plasma were >100 µmol/L (an estimate) and 73.4 µmol/L, respectively. Berotralstat did not affect PT at 10 µmol/L or APTT at 6 µmol/L. These concentrations were, respectively, 35- and 21-fold the mean Cmax after multiple oral administration of berotralstat at the recommended clinical dose (150 mg/day) in humans, i.e. 163 ng/Ml

Safety pharmacology:

1. Effect on central nervous system:

Following a single oral dose of berotralstat 25, 100, or 450 mg/kg to Wistar rats (10 males/group), the effect of berotralstat on the central nervous system was evaluated using the functional observation battery (FOB). There were no deaths or no treatment-related effects on clinical signs or neurobehavioral measurements at any dose level. [14]

2. Effect on respiratory system:

Following a single oral dose of berotralstat 25, 100, or 450 mg/kg to Wistar rats (8 males/group), the effect of berotralstat on the respiratory system was evaluated. There were no deaths or no treatment-related effects on clinical signs or respiratory function (respiratory rate, tidal volume, minute ventilation) at any dose level.

3. Effect on cardiovascular system:

Using cells expressing different human cardiac ion channels, the effects of berotralstat on the ion channel currents were evaluated using the patch-clamp technique. Berotralstat inhibited all ion channels tested concentration-dependently. The effect of berotralstat on the action potentials in isolated rabbit cardiac Purkinje fibers was evaluated. Berotralstat did not prolong the action potential duration (APD) as a surrogate for the QT interval on ECG, at the concentrations of 0.9 to 93.7 µmol/L tested. Other changes in action potentials include decreases in action potential amplitude and in the instant rate of voltage change. At ≥9.4 µmol/L, a depolarized resting membrane potential was observed. Using autonomously beating human iPS cell-derived cardiomyocytes, the effect of berotralstat on the field potential of cardiomyocytes was evaluated. Berotralstat 0.3 µmol/L increased the field potential duration (FPD), a surrogate for the QT interval on ECG, and the corrected field potential duration (FPDc).

4. Effect on various receptors:

The effects of berotralstat on 103 different receptors were evaluated using radioligand binding assays. The *Ki* value was lower than the highest concentration tested of 3 µmol/L at the cannabinoid CB1 receptor,

melanocortin MC5, and somatostatin SST1 receptors only, and the *K*i values were 1.56, 1.92, and 2.09 µmol/L, respectively.

Mechanism of action of berotralstat in preventing HAE attacks:

In patients with HAE, deficient or dysfunctional C1-INH, which inactivates pKal, etc., leads to the activation of the kinin-kallikrein pathway involving pKal. In the kinin-kallikrein pathway, pKal cleaves high-molecular-weight kininogen and releases bradykinin [15]. Free bradykinin causes vasodilatation, enhanced vascular permeability, smooth muscle contraction, etc., leading to clinical symptoms of HAE attacks such as angioedema. In pharmacology studies, berotralstat inhibited pKal, pKal activity in *ex vivo* plasma from healthy subjects and from patients with HAE, and bradykinin production on endothelial cells. Thus, berotralstat is expected to prevent acute attacks of angioedema in patients with HAE by inhibiting pKal [16].

Dosage and administration:

The usual dosage for adult and pediatric patients 12 years of age or older is 150 mg berotralstat (1 capsule) taken orally once daily.

Contraindications:

Hypersensitivity to the active substance.

Special warnings and precautions for use:

1. 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. [17]

2. 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 4.2), or concomitant use of other medicinal products predominantly metabolised by CYP2D6, CYP3A4, or P-gp substrates with a narrow therapeutic index (see section 4.5) or other medicinal products known to prolong the QT (e.g. citalopram, escitalopram, amitriptyline, ondansetron). It is preferable to avoid the use of berotralstat in these patients. If treatment is required, appropriate monitoring (e.g. ECGs) and dose adjustment of these medicinal products should be considered. [18]

3. 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.

Interaction with other medicinal products and other forms of interaction:

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

1. 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%. Berotralstat exposure may be increased with concomitant administration of P-gp and BCRP inhibitors, but no dose adjustment is necessary. [19] Close monitoring for adverse events is recommended for concomitant use with P-gp and BCRP inhibitors such as cyclosporine and grapefruit juice.

- **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.

2. 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.

- **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. [20]

- **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).

- **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).

- **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.

- **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.

Fertility, pregnancy and lactation:

1. 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.

2. 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. Berotralstat is not recommended during pregnancy. [21]

3. Breast-feeding:

Available pharmacodynamic/toxicological data in animals have shown excretion of berotralstat in milk. 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.

4. Fertility:

No effect on fertility was observed in animal studies.

Effects on ability to drive and use machines:

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

Undesirable effects:

1. 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).

CONCLUSION:

Berotralstat is a newly approved kallikrein inhibitor used for the prevention of HAE attacks. Berotralstat 150 mg daily has been proven safe and effective in clinical studies and appears to be a viable oral alternative to parenteral medications currently used in HAE prophylaxis. APeX-S will provide data on much-needed long-term effects of this therapy. However, additional head-to-head studies are still needed to help determine berotralstat's place in true therapy among the other treatment options.

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