orladeyo®
(berotralstat) capsules 150 mg

Phone: 1-866-5-EMPOWER (1-866-536-7693)
Fax: 1-844-336-7693

EMPOWER PATIENT SERVICES

Getting started with ORLADEYO®

- **Sign the consent form** on page 5 to access additional assistance and support.
- **Empower Patient Services will reach out to you by phone** within the next few days for an introductory call and to discuss next steps. **This conversation must take place before your first ORLADEYO shipment.**

Tip: Scan the QR code or save the number for Empower Patient Services (1-866-536-7693) so you don't miss a call.

- You may be eligible to access ORLADEYO while working through insurance approval via the Quick Start program.[a]
- **Schedule a follow-up appointment** within 1 to 2 months (or sooner if needed) to connect with your healthcare provider (in person or virtually) as you start treatment.
- **Stay in touch** with your healthcare provider's office or dedicated care team at Empower Patient Services as treatment questions, concerns, or needs arise.
- Follow your healthcare provider's **daily dosing** instructions when starting treatment.

[a]Subject to terms and conditions of the Quick Start program. BioCryst reserves the right to rescind, revoke, or amend the program at any time without notice.

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EMPOWER PATIENT SERVICES

Complete ORLADEYO® start form checklist

ORLADEYO is administered through Optime Care Specialty Pharmacy, which is part of Empower Patient Services. From initial benefits investigation to delivery, this one care team approach offers you and your patient dedicated support throughout your patient's treatment with ORLADEYO.

Sign and return

- ☐ Prescribing healthcare professional must sign page 3
- ☐ Patient signature requested on page 5
- ☐ Return pages 3 to 5 with documentation outlined below to Empower Patient Services, via fax (1-844-336-7693) or email (info@EmpowerPS.com)

Required documents

It's critical to provide these comprehensive documents **up front** to help with a seamless approval process. Empower Patient Services will consolidate the necessary information for your patient's insurance provider.

- ☐ Both sides of insurance card
- ☐ Both sides of prescription benefit card (if available)
- ☐ Lab results supporting diagnosis of hereditary angioedema (HAE)
  - C1-inhibitor level (antigenic)
  - C1-inhibitor functional
  - C4 level (antigenic)
  - Supportive genetic test results (not required; if available)
- ☐ Up-to-date, detailed chart notes (reference recommended list below)

Recommended chart notes

List is intended as a guide; not all items are required and additional information may be included based on what is available for patient

- Attack history
- Family history
- History of treatment failure, intolerance, or contraindications to other medications
  - Androgens
  - Antifibrinolytics
  - Antihistamines
  - Epinephrine
  - Other HAE prophylactic medications
- Current HAE medications
- Previous HAE medications
- Letter of medical necessity
- Notes from most recent office visit
- Sequelae of attacks (HAE-related hospitalizations, ER visits, and intubations)
- Photos before and after attacks
- Concurrent medications

INDICATION

ORLADEYO® (berotralstat) is a plasma kallikrein inhibitor indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adults and pediatric patients 12 years and older.

Limitations of use

The safety and effectiveness of ORLADEYO for the treatment of acute HAE attacks have not been established. ORLADEYO should not be used for the treatment of acute HAE attacks. Additional doses or dosages of ORLADEYO higher than 150 mg once daily are not recommended due to the potential for QT prolongation.

orladeyo®
(berotralstat) capsules 150 mg

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EMPOWER PATIENT SERVICES

PATIENT INFORMATION

☐ Spanish speaking ☐ Other language

Name (first, middle initial, last): Gender: ☐M ☐F ☐Nonbinary Date of birth (mm/dd/yyyy): / /

Phone: Alternate phone (opt.): Email:

Shipping address: City: State: Zip:

CAREGIVER (OPTIONAL)

Name (first, middle initial, last): Relationship to patient:

Email: Phone:

INSURANCE INFORMATION

Attach both sides of the patient's insurance card and prescription benefit card (if applicable).

☐ Check if patient is uninsured

If you are unable to attach cards, please fill out the information below.

Primary insurance

Subscriber name (first, middle initial, last): Subscriber Date of birth: / /

Relationship of Subscriber to patient: Insurance phone: Policy ID: Group number:

Rx BIN: Rx PCN: Pharmacy plan (if different): Pharmacist help desk phone:

Other insurance (if applicable)

Subscriber name (first, middle initial, last): Subscriber Date of birth: / /

Relationship of Subscriber to patient: Insurance phone: Policy ID: Group number:

Rx BIN: Rx PCN: Pharmacist help desk phone:

If allowed by insurance and with prescriber review and approval, would you like Optime Care to submit the insurance authorization?* ☐ Yes ☐ No

*Optime Care can only use clinical information that is provided directly from the prescriber's office to support insurance authorization.

PRESCRIBER INFORMATION

Specialty and/or designation:

Name (first, middle initial, last): Phone: Email:

Site/office name: Street address: City: State: Zip:

NPI: State license number: Supervising physician name (if NP/PA):

Office contact

Preferred contact name (first, middle initial, last): Office phone: Fax:

Email: Preferred method of contact (select all that apply): ☐ Phone ☐ Email ☐ Fax

ORLADEYO PRESCRIPTION INFORMATION

Diagnosis: ☐ ICD-10 D84.1 (HAE) ☐ Other (please specify) _____

Dose: 1 (one) capsule orally, once daily with food.† Select 1 dose: ☐ 150 mg ☐ 110 mg

†You may also start appropriate patients at a reduced dosage of 110 mg once daily and adjust to 150 mg once daily when necessary.

Please see accompanying full Prescribing Information for additional details.

Supply: Dispense quantity of 28 capsules (4-week supply) **Refills (select one):** ☐ 12 ☐ Other _____

Special precautions (e.g., allergies):

Customized dosing directions:

Directions for transitioning from prior HAE therapy:

☐ If eligible and when all information required for prior authorization is received, I request for my patient to participate in the Quick Start program that will provide free drug during the insurance approval process. The Quick Start program is available to all insured patients ≥12 years of age who are US residents with a confirmed diagnosis of HAE. Eligibility is subject to the terms and conditions of the program. BioCryst reserves the right to rescind, revoke, or amend the program at any time without notice. Contact Empower Patient Services for details.

PRESCRIBER SIGNATURE (STAMPS NOT ACCEPTABLE)

New York prescribers—please submit prescription on an original NY state prescription blank.

By signing below, I certify that (a) the above therapy is medically necessary and that I will supervise the patient's treatment accordingly; (b) I have received the necessary authorizations, including those required by state law and the Health Insurance Portability and Accountability Act of 1996 (HIPAA), to release the above information and other health and medical information of the patient to the dispensing pharmacy.

Signature (dispense as written): Date:

Signature (substitutions permitted): Date:

orladeyo® (berotralstat) capsules 150 mg

EMPOWER PATIENT SERVICES

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AUTHORIZATION FOR USE AND DISCLOSURE OF PERSONAL HEALTH INFORMATION

I authorize Optime Care, Inc. ("Optime") to share my, or my legal dependent's, as applicable, personal health information ("PHI"), including, but not limited to, my medical diagnosis, condition, treatment (including prescription information), health insurance information, financial information, demographic information, and contact information, whether provided to Optime previously or in the future, with BioCryst Pharmaceuticals, Inc. (including its representatives and service providers) ("BioCryst").

I authorize such disclosures so that BioCryst may use my PHI for the following purposes:

- to provide product support services for ORLADEYO, including, but not limited to, copay assistance, reimbursement support, and other forms of patient assistance
- to communicate with me by mail, email, text message, telephone, or other means about my medical condition, treatment, care management, and health insurance
- for reimbursement support
- for investigating insurance coverage including coordination of benefits

I authorize such disclosures so that BioCryst, and its agents may use my PHI for the following purposes:

- to evaluate patient experiences and product services, and to improve current and future products and services
- to contact me about my interest in participating in market research
- to contact me about participation in a mentor program

I authorize BioCryst and Optime to use my PHI for these purposes and to share my PHI in connection with these purposes, including with my healthcare providers, insurance providers, and pharmacy, and their representatives, in order for them to coordinate my benefits, provide, when applicable, reimbursement support, investigate my insurance coverage, coordinate shipments of dispensed drug and help with financial assistance for BioCryst products.

I also authorize Optime, BioCryst, and its agents to share my PHI related to my HAE condition and treatment with the patient support organizations related to HAE ("Support Organizations"), including their representatives and service providers.

I authorize such disclosures so that Support Organizations may use my PHI for the purposes listed above.

I understand that once my PHI is shared, the information could be re-disclosed, but that the intent is to use my PHI only for the purposes listed above. I understand that I do not have to sign this Authorization in order to receive healthcare, payment for healthcare, or to be eligible for healthcare benefits.

orladeyo
(berotralstat) capsules 150 mg

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This Authorization expires 20 years from the date of my signature below, unless otherwise required by law.

I agree that if I reside in the state of Maryland, this form will be valid for no longer than 1 year from the date signed.

If I reside in California, I also have the right to request that BioCryst and/or Support Organizations delete my PHI, although deletion is not required under certain circumstances. To cancel or request deletion, I must send a written notice to BioCryst at 4050 Emperor Blvd. Suite 200, Durham, NC 27703. If I cancel and request deletion, I know that BioCryst and Service Providers will no longer be able to assist me with access to ORLADEYO.

I have the right to cancel this Authorization. If I cancel, this means that BioCryst and/or Support Organizations will no longer use or share my PHI. This will not apply to PHI already used or shared or when it is required by law.

I understand that I may revoke this Authorization by sending a written notice of revocation to Optime Care at 4060 Wedgeway Court, Earth City, MO 63045. Notice may also be sent via fax to (844) 336-7693. I understand that if I do revoke the Authorization, that will not invalidate any uses or disclosures of my PHI made in reliance on the Authorization prior to the receipt by Optime, BioCryst, and Support Organizations of my notice of revocation.

I understand that I am entitled to receive a copy of this Authorization over the time it is valid. I certify that I am at least eighteen (18) years of age.

By signing below, I certify that I have read and agree to the above.

_____ _____

Patient signature *Date*

Patient full signature is required. No stamps.

Patient printed name

If being signed by authorized representative, please sign below and describe your relationship to patient

_____ _____

Signature *Date*

Patient's legally authorized representative signature (if applicable)

First name Last name

Relationship to the patient

orladeyo® (berotralstat) capsules 150 mg

Phone: 1-866-5-EMPOWER (1-866-536-7693)
Fax: 1-844-336-7693

EMPOWER PATIENT SERVICES

What to expect next

1. Once the start form and chart notes (refer to checklist on page 2) have been submitted, Empower Patient Services will confirm receipt via email or fax, depending on office preference, and follow up with your office if additional documentation is required.
2. Encourage your patient to schedule a check-in within 1 to 2 months of starting treatment, or sooner if needed.
3. Empower Patient Services (1-866-536-7693) will reach out to your patient for an introductory call and to discuss next steps.
4. If applicable, your Empower Patient Services contact will assess your patient's eligibility for the Quick Start program, financial assistance, and support programs.
5. Your dedicated care coordinator will work alongside you, your office, and your patient throughout the entire approval process as well as provide ongoing support after initiation of treatment with ORLADEYO®.

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ORLADEYO® safely and effectively. See full prescribing information for ORLADEYO.

ORLADEYO (berotralstat) capsules, for oral use
Initial U.S. Approval: 2020

----------INDICATIONS AND USAGE----------
ORLADEYO is a plasma kallikrein inhibitor indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adults and pediatric patients 12 years and older. (1)

Limitations of Use:
ORLADEYO should not be used for treatment of acute HAE attacks. (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended Dosage: One capsule (150 mg) taken orally once daily with food. (2.1)

See Full Prescribing Information for:
- Dosage adjustment in patients with moderate or severe hepatic impairment. (2.2)
- Dosage adjustment in patients with chronic administration of P-gp or BCRP inhibitors. (2.3)
- Dosage adjustment in patients with persistent gastrointestinal reactions. (2.4)

----------DOSAGE FORMS AND STRENGTH----------
Capsules: 150 mg, 110 mg (3)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
An increase in QT prolongation can occur at dosages higher than the recommended 150 mg once daily dosage. Additional doses or doses of ORLADEYO higher than 150 mg once daily are not recommended. (5.1)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥10%) are abdominal pain, vomiting, diarrhea, back pain, and gastroesophageal reflux disease. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact BioCryst Pharmaceuticals, Inc. at 1-833-633-2279 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
P-gp or BCRP inhibitors: Reduce ORLADEYO dosage when co-administered. (7.1, 12.3)

P-gp inducers: Avoid use with ORLADEYO. (7.1)

CYP2D6, CYP3A4 or P-gp Substrates: Appropriately monitor or dose titrate narrow therapeutic index drugs that are predominantly metabolized by CYP2D6, CYP3A4 or are P-gp substrates when co-administered with ORLADEYO. (7.2, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ORLADEYO® is indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adults and pediatric patients 12 years of age and older.

Limitations of Use:
The safety and effectiveness of ORLADEYO for the treatment of acute HAE attacks have not been established. ORLADEYO should not be used for treatment of acute HAE attacks. Additional doses or doses of ORLADEYO higher than 150 mg once daily are not recommended due to the potential for QT prolongation *[see Warnings and Precautions (5.1)].*

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of ORLADEYO is one 150 mg capsule taken orally once daily with food.

2.2 Recommended Dosage in Patients with Hepatic Impairment

No dosage adjustment of ORLADEYO is recommended for patients with mild hepatic impairment (Child-Pugh Class A) *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

In patients with moderate or severe hepatic impairment (Child-Pugh B or C), the recommended dosage of ORLADEYO is one 110 mg capsule taken orally once daily with food *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

2.3 Recommended Dosage for Concomitant Use with P-gp or BCRP Inhibitors

In patients with chronic administration of P-gp or BCRP inhibitors (e.g., cyclosporine), the recommended dosage of ORLADEYO is one 110 mg capsule taken orally once daily with food *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

2.4 Dosage Adjustment in Patients with Persistent GI Reactions

Gastrointestinal (GI) reactions may occur in patients receiving ORLADEYO *[see Adverse Reactions (6.1)]*. If GI events persist, a reduced dose of 110 mg once daily with food may be considered.

3 DOSAGE FORMS AND STRENGTHS

Capsules:

- 150 mg: a white opaque body with a black imprint “150” and a light blue opaque cap with a black imprint “BCX”.
- 110 mg: light blue opaque capsules with a white imprint “110” on body and a white imprint “BCX” on cap.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Risk of QT Prolongation with Higher-Than-Recommended Dosages

ORLADEYO should not be used for treatment of acute attacks of HAE. Additional doses or doses of ORLADEYO higher than 150 mg once daily are not recommended. An increase in QT was observed at dosages higher than the recommended 150 mg once daily dosage and was concentration dependent *[see Clinical Pharmacology (12.2)].*

6 ADVERSE REACTIONS

The following clinically significant adverse reaction is described elsewhere in the labeling:

- QT Prolongation *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of ORLADEYO is primarily based on 24-week (Part 1) data from a 3-part, double-blind, parallel-group, placebo-controlled study (Trial 1) in 120 patients with Type I or II HAE randomized and dosed with either ORLADEYO 110 mg, 150 mg or placebo, once daily with food. After Week 24, patients who continued in the study received active treatment through 48 weeks.

In Trial 1, a total of 81 patients aged 12 years and older with HAE received at least one dose of ORLADEYO 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 study drug prematurely due to adverse reactions was 7% and 3% for patients treated with 110 mg and 150 mg ORLADEYO, respectively, and 3% for placebo-treated patients. No deaths occurred in the trial.

The safety profile of ORLADEYO was generally similar across all subgroups of patients, including analysis by age, sex, and geographic region.

Table 1 shows adverse reactions occurring in ≥10% of patients in any ORLADEYO treatment group that also occurred at a higher rate than in the placebo treatment group in Trial 1.

Table 1: Adverse Reactions Observed in ≥10% of Patients in any ORLADEYO Treatment Group (Trial 1)

Adverse Reaction	Placebo (N=39)	ORLADEYO		
		110 mg (N=41)	150 mg (N=40)	Total (N=81)
	n (%)	n (%)	n (%)	n (%)
Abdominal Pain*	4 (10)	4 (10)	9 (23)	13 (16)
Vomiting	1 (3)	4 (10)	6 (15)	10 (12)
Diarrhea†	0	4 (10)	6 (15)	10 (12)
Back Pain	1 (3)	1 (2)	4 (10)	5 (6)
Gastroesophageal Reflux Disease	0	4 (10)	2 (5)	6 (7)

* includes Abdominal pain, Abdominal discomfort, Abdominal pain upper, and Abdominal tenderness

† includes Diarrhea and Frequent bowel movements

Gastrointestinal reactions, including abdominal pain, vomiting, and diarrhea occurred more frequently in patients receiving ORLADEYO 150 mg versus ORLADEYO 110 mg or placebo. These reactions generally occurred early after initiation of treatment with ORLADEYO, became less frequent with time, and typically self-resolved. No patients in the ORLADEYO 150 mg dose group and 1 patient in the ORLADEYO 110 mg dose group discontinued treatment due to a gastrointestinal adverse reaction.

Less Common Adverse Reactions

Other adverse reactions that occurred in Part 1 of Trial 1 with an incidence between 5% and <10% at a higher incidence in ORLADEYO-treated patients compared to placebo included headache (9% versus 5%), fatigue (6% versus 3%), and flatulence (6% versus 3%).

A maculopapular drug rash was reported in less than 1% of patients treated with ORLADEYO. The rash resolved, including in subjects who continued dosing.

Safety data are also available from 227 patients enrolled in an ongoing, open-label, long-term safety study (Trial 2) who received ORLADEYO 110 mg (N=100) or 150 mg (N=127) once daily with food and are consistent with the 24-week controlled safety data from Trial 1 (Part 1).

Laboratory Abnormalities

Transaminase elevations

In Part 1 of Trial 1, a single 150 mg ORLADEYO-treated patient discontinued treatment due to asymptomatic elevated transaminases (ALT >8x the upper limit of normal [ULN] and AST >3x ULN). Total bilirubin was normal. No subject receiving 110 mg or placebo developed transaminase levels >3x ULN. In addition to this patient, 2 ORLADEYO-treated patients developed laboratory-related hepatic adverse events compared to 1 placebo-treated patient. No patient reported serious adverse reactions of elevated transaminases.

7 DRUG INTERACTIONS

This section describes clinically relevant drug interactions with ORLADEYO. Drug interaction studies are described elsewhere in the labeling *[see Clinical Pharmacology (12.3)].*

7.1 Potential for Other Drugs to Affect ORLADEYO

P-gp or BCRP inhibitors

ORLADEYO is a P-gp and BCRP substrate. A dose of 110 mg ORLADEYO is recommended for patients with chronic administration of P-gp or BCRP inhibitors (e.g., cyclosporine) *[see Clinical Pharmacology (12.3)].*

P-gp Inducers

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

7.2 Potential for ORLADEYO to Affect Other Drugs

CYP2D6 and CYP3A4 Substrates

ORLADEYO at a dose of 150 mg is a moderate inhibitor of CYP2D6 and CYP3A4. For concomitant medications with a narrow therapeutic index that are predominantly metabolized by CYP2D6 (e.g., thioridazine, pimozide) or CYP3A4 (e.g., cyclosporine, fentanyl), appropriate monitoring and dose titration is recommended *[see Clinical Pharmacology (12.3)]*.

P-gp Substrates

ORLADEYO at a dose of 300 mg is a P-gp inhibitor. Appropriate monitoring and dose titration is recommended for P-gp substrates (e.g., digoxin) when co-administering with ORLADEYO *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are insufficient data in pregnant women available to inform drug-related risks with ORLADEYO use in pregnancy. Based on animal reproduction studies, no evidence of structural alterations was observed when berotralstat was administered orally to pregnant rats and rabbits during organogenesis at doses up to approximately 10 and 2 times, respectively, the maximum recommended human daily dose (MRHDD) in adults on an AUC basis (*see Data)*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In animal reproduction studies, oral administration of berotralstat to pregnant rats and rabbits during the period of organogenesis did not cause fetal structural alterations. The berotralstat dose in rats and rabbits was up to approximately 10 and 2 times, respectively, the MRHDD in adults (on an AUC basis at maternal doses of 75 and 100 mg/kg/day, respectively). In a pre- and postnatal development study in rats, oral administration of berotralstat to pregnant rats during the period of organogenesis and until delivery at doses up to 45 mg/kg/day (approximately 2 times of the MRHDD on a mg/m^2 basis) did not cause fetal structural alterations either. Berotralstat concentrations in the fetal blood were approximately 5-11% of the maternal blood.

8.2 Lactation

Risk Summary

There are no data on the presence of berotralstat in human milk, its effects on the breastfed infant, or its effects on milk production. However, when a drug is present in animal milk, it is likely that the drug will be present in human milk. Low levels of berotralstat were detected in the plasma of rat pups when dams were dosed with the drug orally during the lactation period. The berotralstat concentration in the pup plasma was approximately 2% of the maternal plasma *(see Data)*.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ORLADEYO and any potential adverse effects on the breastfed infant from ORLADEYO or from the underlying maternal condition.

Data

Animal Data

In the pre- and post-natal development study in rats, berotralstat was administered to dams during the pregnancy and lactation periods at doses up to 45 mg/kg/day (approximately 2 times of the MRHDD on a mg/m^2 basis). Berotralstat was detected in the plasma of pups during the lactation period. The berotralstat concentration in the pup plasma was approximately 2% of the maternal plasma. Both dams and pups at 45 mg/kg/day showed statistically significant decreases in body weight gain ($p<0.05$). No treatment-related effects were observed at 25 mg/kg/day (approximately equal to the MRHDD on a mg/m^2 basis).

8.4 Pediatric Use

The safety and effectiveness of ORLADEYO for prophylaxis to prevent attacks of hereditary angioedema have been established in pediatric patients aged 12 and older. Use of ORLADEYO in this population is supported by evidence from an adequate and well-controlled study (Trial 1) that included adults and a total of 6 adolescent patients aged 12 to <18 years of age. The safety profile

and attack rate on study were similar to those observed in adults *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]*. An additional 10 adolescent patients aged 12 to <18 years were enrolled in the open-label study (Trial 2).

The safety and effectiveness of ORLADEYO in pediatric patients <12 years of age have not been established.

8.5 Geriatric Use

The safety and effectiveness of ORLADEYO were evaluated in a subgroup of patients (N=9) aged ≥65 years in Trial 1. Results of the subgroup analysis by age were consistent with overall study results. The safety profile from an additional 5 elderly patients aged ≥65 years enrolled in the open-label, long-term safety study (Trial 2) was consistent with data from Trial 1 *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

8.6 Renal Impairment

No dosage adjustment of ORLADEYO is recommended for patients with mild, moderate or severe renal impairment *[see Clinical Pharmacology (12.3)]*.

ORLADEYO has not been studied in patients with End-Stage Renal Disease (CL_{CR} <15 mL/min or eGFR <15 mL/min/1.73 m^2 or patients requiring hemodialysis), and therefore is not recommended for use in these patient populations *[see Clinical Pharmacology (12.3)].*

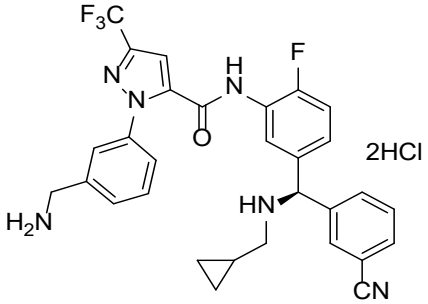
8.7 Hepatic Impairment

No dosage adjustment of ORLADEYO is recommended for patients with mild hepatic impairment (Child-Pugh Class A) *[see Clinical Pharmacology (12.3)]*.

In patients with moderate or severe hepatic impairment (Child-Pugh B or C), the recommended dose of ORLADEYO is 110 mg once daily with food *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

ORLADEYO (berotralstat) capsules is a plasma kallikrein inhibitor. Berotralstat is presented as the dihydrochloride salt with the chemical name 1-[3-(aminomethyl)phenyl]-*N*-(5-{(*R*)-(3-cyanophenyl)[(cyclopropylmethyl)amino]methyl}-2-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide dihydrochloride. The chemical structure is:



Berotralstat dihydrochloride is a white to off-white powder that is soluble in water at pH ≤4. The molecular formula is $C_{30}H_{26}F_4N_6O$ • 2HCl and the molecular weight is 635.49 (dihydrochloride).

ORLADEYO is supplied as 150 mg (equivalent to 169.4 mg berotralstat dihydrochloride) and 110 mg (equivalent to 124.3 mg berotralstat dihydrochloride) hard gelatin capsules for oral administration. Each capsule contains the active ingredient berotralstat dihydrochloride and the inactive ingredients colloidal silicon dioxide, crospovidone, magnesium stearate, and pregelatinized starch.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Berotralstat is a plasma kallikrein inhibitor that binds to plasma kallikrein and inhibits its proteolytic activity. Plasma kallikrein is a protease that cleaves high-molecular-weight-kininogen (HMWK) to generate cleaved HMWK (cHMWK) and bradykinin, a potent vasodilator that increases vascular permeability resulting in swelling and pain associated with HAE. In patients with HAE due to C1-inhibitor (C1-INH) deficiency or dysfunction, normal regulation of plasma kallikrein activity is not present, which leads to uncontrolled increases in plasma kallikrein activity and results in angioedema attacks. Berotralstat decreases plasma kallikrein activity to control excess bradykinin generation in patients with HAE.

12.2 Pharmacodynamics

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

Cardiac Electrophysiology

At the recommended dose of 150 mg once daily, ORLADEYO does not prolong the QT interval to any clinically relevant extent. At 3-times the recommended dose, the mean (upper 90% confidence interval) increase in QTcF was 15.9 msec (23.5 msec). The observed increase in QTcF was concentration-dependent.

12.3 Pharmacokinetics

Following oral administration of berotralstat 150 mg once daily, the steady state 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*hr/mL (range: 1880 to 3790 ng*hr/mL), respectively. Following oral administration of berotralstat 110 mg once daily, the steady-state C_{max} and AUC_{tau} are 97.8 ng/mL (range: 63 to 235 ng/mL) and 1600 ng*hr/mL (range: 950 to 4170 ng*hr/mL), respectively.

Berotralstat exposure (C_{max} and AUC) increases greater than proportionally with dose and steady state is reached by days 6 to 12. After once-daily administration, exposure of berotralstat at steady state is approximately 5 times that after a single dose.

The pharmacokinetics of berotralstat are similar between healthy adult subjects and in patients with HAE.

Absorption

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

Effect of Food

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 radiolabeled berotralstat 300 mg, the blood to plasma ratio was approximately 0.92.

Elimination

The median elimination half-life of berotralstat was approximately 93 hours (range: 39 to 152 hours).

Metabolism

Berotralstat is metabolized by CYP2D6 and by CYP3A4 with low turnover *in vitro*. After a single oral radiolabeled 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.

Excretion

After a single oral radiolabeled berotralstat 300 mg dose, approximately 9% was excreted in urine (3.4% unchanged; range: 1.8 to 4.7%) and 79% was excreted in feces.

Specific Populations

Body weight, age, gender, and race did not have a clinically meaningful influence on the systemic exposure of berotralstat.

Geriatric Patients

Based on the population pharmacokinetic analyses that included elderly patients (≥65 to 74 years, N=25), age does not have a clinically meaningful impact on the systemic exposure of berotralstat *[see Use in Specific Populations (8.5)]*.

Pediatric Patients

Based on population pharmacokinetic analyses that included pediatric patients 12 to <18 years of age, exposure at steady state following oral administration of berotralstat 150 mg once daily was approximately 20% higher compared to adults. The higher exposure in adolescents is not considered to be clinically meaningful.

Patients with Renal Impairment

The pharmacokinetics of a single 200 mg oral dose of berotralstat were studied in subjects with severe renal impairment (CL_{CR} less than 30 mL/min). When compared to a concurrent cohort with normal renal function (CL_{CR} greater than 90 mL/min), no clinically relevant differences were observed; C_{max} was increased by 47%, while $AUC_{0\text{-last}}$ was increased by 14% *[see Use in Specific Populations (8.6)]*.

The pharmacokinetics of berotralstat has not been studied in patients with End-Stage Renal Disease (CL_{CR} less than 15 mL/min or eGFR less than 15 mL/min/1.73 m^2 or patients requiring hemodialysis).

Patients with Hepatic Impairment

The pharmacokinetics of a single 150 mg oral dose of berotralstat were studied in subjects with mild, moderate, and severe hepatic function (Child-Pugh Class A, B, and C, respectively). The pharmacokinetics of berotralstat were unchanged in subjects with mild hepatic impairment compared to subjects with normal hepatic function. In subjects 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 $AUC_{0\text{-last}}$ was decreased by 5%. The median half-life of berotralstat was increased by 37% and 22% in patients with moderate and severe hepatic impairment, respectively, in comparison to healthy subjects. The percent of unbound berotralstat increased 2-fold from a mean of 1.2% in healthy subjects to a mean of 2.4% in subjects with severe hepatic impairment *[see Use in Specific Populations (8.7)]*.

Drug Interaction Studies

Effect of Other Drugs on the Pharmacokinetics of ORLADEYO

Berotralstat is a P-gp and BCRP substrate. Cyclosporine, a P-gp and BCRP inhibitor, increased berotralstat C_{max} by 25%, $AUC_{0\text{-last}}$ by 55%, and $AUC_{0\text{-inf}}$ by 69% *[see Drug Interactions (7.1)]*.

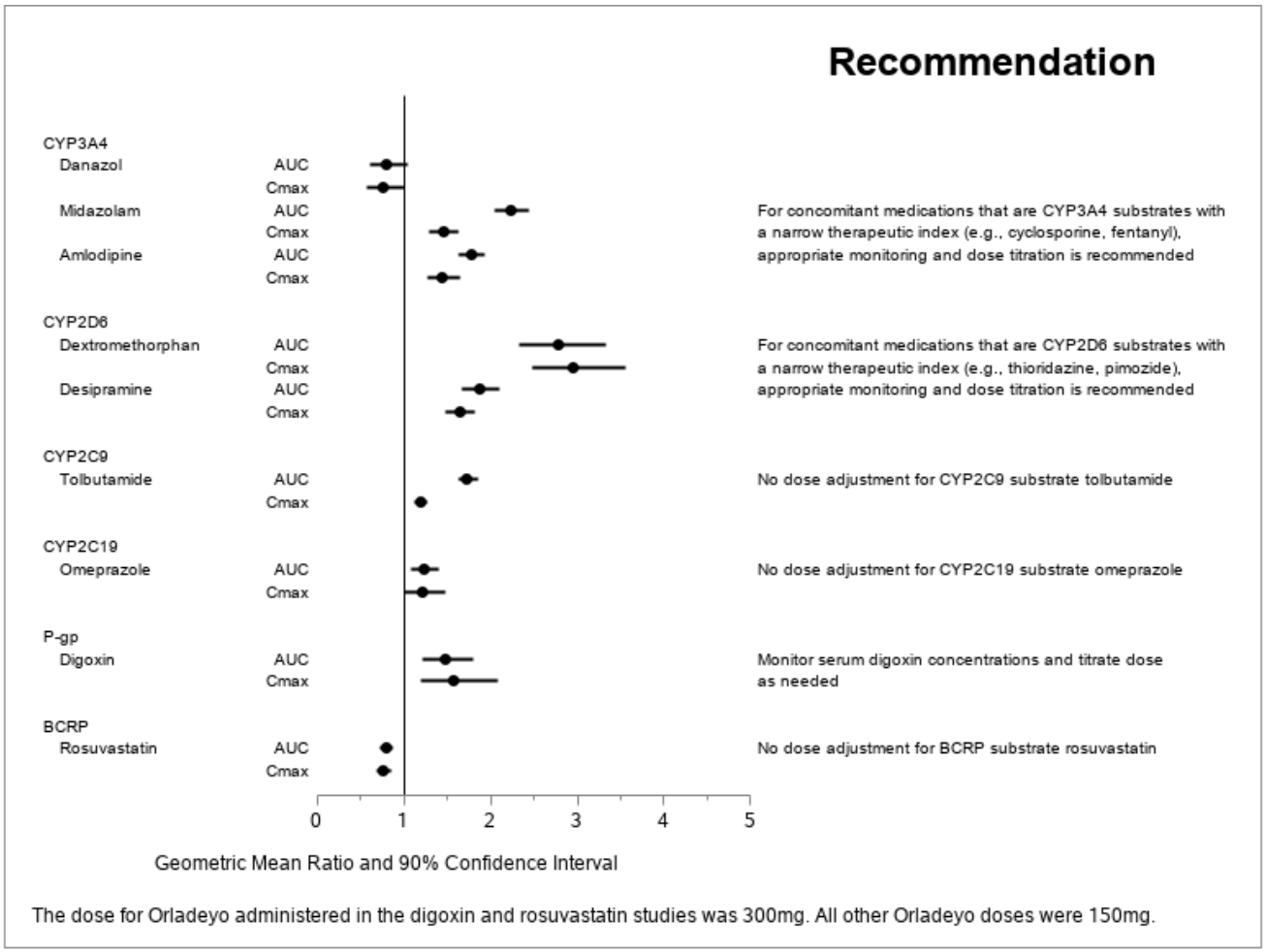
Effect of ORLADEYO on the Pharmacokinetics of Other Drugs

Berotralstat 150 mg once daily is a moderate inhibitor of CYP2D6 and CYP3A4, and a weak inhibitor of CYP2C9 and CYP2C19.

Berotralstat at a 300 mg dose is an inhibitor of P-gp and is not an inhibitor of BCRP (rosuvastatin exposure was decreased by approximately 20%).

The effect of berotralstat on the pharmacokinetics of other drugs are presented in Figure 1 *[see Drug Interactions (7.2)].*

Figure 1: Effect of ORLADEYO on Concomitant Medications



13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity of berotralstat was evaluated in a 2-year study in Wistar rats and a 26-week study in Tg.rasH2 transgenic mice. The berotralstat doses (oral gavage) were up to 20 and 50 mg/kg/day in rats and mice (approximately 5 and 10 times the MRHDD on a plasma AUC basis, respectively). No evidence of tumorigenicity was observed in either species.

Mutagenesis

Berotralstat tested negative in the *in vitro* bacterial reverse mutation assay (Ames test), the *in vitro* chromosomal aberration assay in human peripheral blood lymphocytes, and the *in vivo* rat micronucleus assay.

Impairment of Fertility

In a fertility study in rats, berotralstat at oral doses up to 45 mg/kg/day (approximately 2 times the MRHDD on a mg/m^2 basis) showed no effect on fertility in males or females.

14 CLINICAL STUDIES

Trial 1 (NCT3485911)

The efficacy of ORLADEYO for the prevention of angioedema attacks in patients 12 years of age and older with Type I or II HAE was demonstrated in Part 1 of a multicenter, randomized, double-blind, placebo-controlled, parallel-group study (Trial 1).

The study included 120 adult and adolescent patients 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. Patients were randomized 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).

Patients discontinued other prophylactic HAE medications prior to entering the study; however, all patients were allowed to use rescue medications for treatment of breakthrough HAE attacks.

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/month. Seventy percent of patients enrolled had a baseline attack rate of ≥2 attacks/month.

ORLADEYO 150 mg and 110 mg produced statistically significant reductions in the rate of HAE attacks compared to placebo for the primary endpoint in the Intent-to-Treat (ITT) population as shown in Table 2. The percent reductions in HAE attack rate were greater with ORLADEYO 150 mg and 110 mg relative to placebo, regardless of attack rate during the run-in period.

Table 2. Primary Efficacy Endpoint (Trial 1): Reduction in HAE Attack Rate- ITT Population

	ORLADEYO		Placebo
	110 mg QD	150 mg QD	
Outcome	**N = 41**	**N = 40**	**N = 40***
HAE Attack Rate, rate per 28 days†	1.65	1.31	2.35
% Rate Reduction ‡ (95% CI)	30.0% (4.6, 48.7)	44.2% (23.0, 59.5)	-
p-value	0.024	<0.001	-

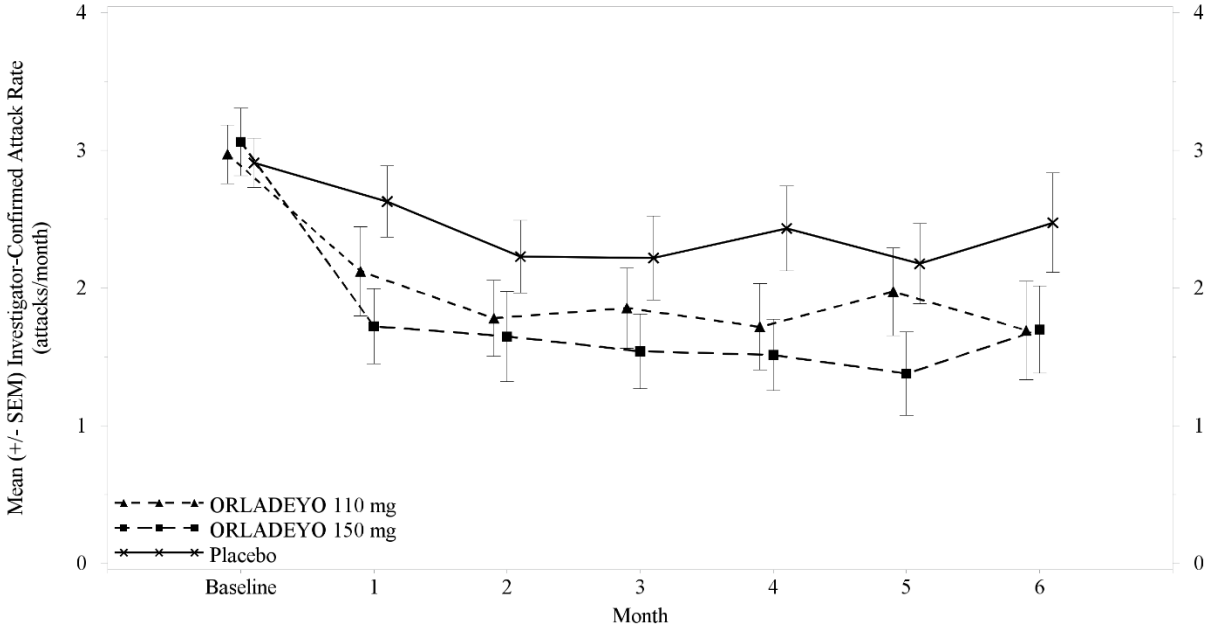
* One patient in the ITT analysis was randomized to placebo but was not treated.

† Statistical analysis based on a negative binomial regression model; number of attacks included as dependent variable, treatment included as fixed effect, baseline attack rate included as covariate, and logarithm of duration on treatment included as offset variable.

‡ Percent reduction relative to placebo.

Reductions in attack rates were observed in the first month of treatment with ORLADEYO 150 mg and 110 mg and were sustained through 24 weeks as shown in Figure 2.

Figure 2. Mean (+/- SEM) HAE Attack Rate/month Through 24 Weeks (Trial 1)- ITT Population



Pre-defined exploratory endpoints included the proportion of responders to study drug, defined as at least a 50% relative reduction in HAE attacks during treatment compared with the baseline attack rate; 58% of patients receiving 150 mg ORLADEYO and 51% of patients receiving 110 mg ORLADEYO 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 150 mg ORLADEYO, and 27% and 10% of patients receiving 110 mg ORLADEYO, had a ≥70% or ≥90% reduction in their HAE attack rates compared to baseline versus 15% and 8% of placebo patients, respectively. The rate of attacks rated as moderate or severe was reduced by 40% and 10% in patients receiving 150 mg ORLADEYO and 110 mg ORLADEYO, respectively, versus placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

ORLADEYO (berotralstat) capsules:

- 150 mg: a white opaque body with a black imprint “150” and a light blue opaque cap with a black imprint “BCX”.
- 110 mg: light blue opaque capsules with a white imprint “110” on body and a white imprint “BCX” on cap.
- A 28-day supply of ORLADEYO is provided in a carton containing four child-resistant shellpaks, each containing a 7-capsule blister card. NDC 72769-101-01 (150 mg) and NDC 72769-102-01 (110 mg).
- Each carton contains a tamper evident seal.
- Do not use if tamper evident seal is broken or missing.

Store at 20ºC to 25ºC (68ºF to 77ºF). Excursions permitted between 15ºC and 30ºC (59ºF to 86ºF) *[see USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Inform patients of the risks and benefits of ORLADEYO before prescribing or administering to the patient.

Drug Interactions

Advise patients that ORLADEYO may interact with other drugs *[see Drug Interactions (7) and Clinical Pharmacology (12.3)]*. Advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products.

Not for Acute Treatment of HAE Attacks

Advise patients to take their usual rescue medication to treat an acute attack of HAE. Inform patients that the safety and effectiveness of ORLADEYO has not been established as an acute treatment for HAE attacks. Advise patients that they should not take daily doses higher than 150 mg once daily or additional doses of ORLADEYO to treat an acute attack of HAE due to risk of QT prolongation *[see Limitations of Use (1) and Warnings and Precautions (5.1)].*

For more information, visit www.ORLADEYO.com

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Manufactured for:
BioCryst Pharmaceuticals, Inc.
Durham, NC 27703

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