Hereditary angioedema (HAE)

attack prevention doesn't need to be complicated.

ORLADEYO® offers significant attack rate reduction, a convenient daily capsule, and long-term safety data.[1,2]

Capsule not actual size

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.

Please see Important Safety Information on page 13 and accompanying full Prescribing Information.

orladeyo®
(berotralstat) capsules 150 mg

BioCryst®

orladeyo®
(berotralstat) capsules 150 mg

Patients with HAE are likely struggling with disease and treatment burden[3,4]

Self-administration challenges, needle fatigue, and other issues may be weighing patients down[3]

In a study of 75 adults living with HAE, approximately 90% of patients say they have learned to **tolerate** difficult aspects of their treatment, while 75% of patients say they **try not to think about** the demanding nature of their treatment.[3]

With the treatment landscape changing, you can talk with your patients about their satisfaction with their current therapy and what approach might best meet their needs.

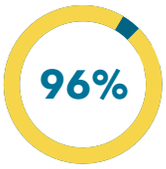
Prophylactic therapy should be determined based on individual considerations[4,5]:

- Disease-related factors (physical, emotional, quality of life)
- Treatment-related factors (route of administration, side effects, availability/supply)
- Patient preference (lifestyle, dosing schedule, flexibility)

Research shows there is a strong patient demand for an oral prophylactic therapy[6]

Data from a study of 75 patients with HAE demonstrate the preference for an oral preventative therapy.[6]

of the 48 patients on a prophylactic therapy would **prefer an oral treatment** if one were available even though they are satisfied with their current prophylactic therapy[6]



of the 48 patients on a prophylactic therapy agree that an **oral prophylactic therapy would better fit their lives** vs an injectable HAE medication[6]

Shared decision making empowers patients to play a more active role in treatment decisions and be more compliant with their treatment, leading to better overall outcomes.[7]

orladeyo®
(berotralstat) capsules 150 mg

ORLADEYO® is the first and only targeted oral prophylactic therapy for HAE[1]

ORLADEYO offers the convenient oral administration your patients have hoped for[1,6]

As a single 150 mg[a] capsule taken once daily with food, ORLADEYO provides simple and straightforward dosing and administration without the need for cumbersome supplies and storage.[1]

Oral administration

No need for injection, infusion, or related supplies[1]

Flexibility

May be taken anywhere and at any time, at the same time each day, with food[1,8]

Easy storage

Room temperature; no refrigeration required[1]

ORLADEYO offers the consistency of daily dosing with the simplicity of oral administration.[1,a]

[a] A reduced dosage of 110 mg taken orally once daily with food is recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C) and in patients taking chronically administered P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) inhibitors (eg, cyclosporine).[1]

SELECT IMPORTANT SAFETY INFORMATION

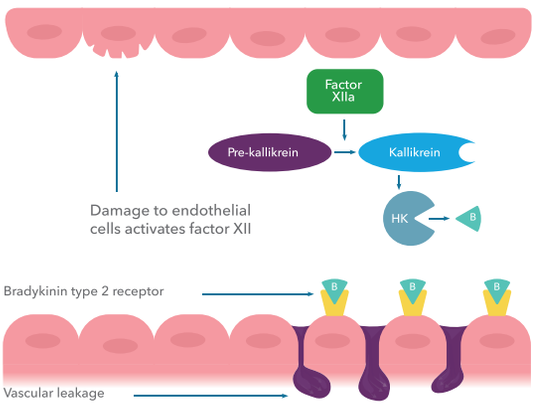
An increase in QT prolongation was observed at dosages higher than the recommended 150 mg once-daily dosage and was concentration dependent.

Please see Important Safety Information on page 13 and accompanying full Prescribing Information.

orladeyo®
(berotralstat) capsules 150 mg

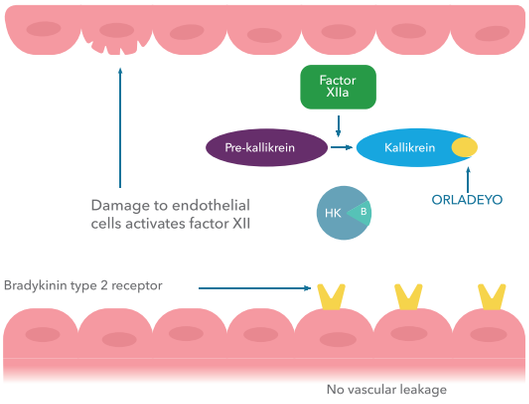
ORLADEYO®: a daily capsule that targets and inhibits plasma kallikrein[1]

Untreated HAE[9,10]



In HAE, uncontrolled plasma kallikrein activity triggers an overproduction of bradykinin, which leads to vasodilation, vascular leakage, and subsequent swelling.

With ORLADEYO[1,9,10]



By decreasing plasma kallikrein activity, ORLADEYO prevents the cleavage of HK and subsequent release of bradykinin, ultimately preventing HAE attacks.

Abbreviations: B, bradykinin; factor XIIa, activated factor XII; HK, high-molecular–weight kininogen.

ORLADEYO was studied in one of the largest clinical studies for a prophylactic therapy in HAE[1,11]

APeX-2 is a 3-part, double-blind, placebo-controlled study[1]

Participants[11]	121 patients (≥12 years of age) with confirmed HAE type 1 or 2 who experienced ≥2 investigator-confirmed attacks during the 8-week run-in period[a]		
Length of study[2,11,12]	Part 1 (randomized 1:1:1)	Part 2 (dose blinded)[b]	Part 3 (open label)
	24 weeks (day 1-week 24)	24 weeks (week 24-48)	48 weeks (week 48-96)
Daily dosing regimen[2,11,12]	Berotralstat 150 mg, berotralstat 110 mg, or placebo	Berotralstat 150 mg or berotralstat 110 mg	Berotralstat 150 mg

[a]Patients were allowed to use rescue medications to treat attacks but had to discontinue all prophylactic HAE medications prior to the start of the study.[11]

[b]In part 2 of the study, patients on active drug in part 1 continued on the same dose and patients on placebo in part 1 were rerandomized to a blinded active dose.[12]

SELECT IMPORTANT SAFETY INFORMATION

The most common adverse reactions (≥10% and higher than placebo) in patients receiving ORLADEYO were abdominal pain, vomiting, diarrhea, back pain, and gastroesophageal reflux disease.

Please see Important Safety Information on page 13 and accompanying full Prescribing Information.

orladeyo®
(berotralstat) capsules 150 mg

Patients in APeX-2 had considerable disease burden and a history of past prophylactic treatment use[8]

Demographics and baseline characteristics of intent-to-treat population (N=121)[8]	
Median age (min, max)	40 (12, 74)
Female, n (%)	80 (66%)
Median baseline investigator-confirmed attack rate, attacks/month (range)[a]	2.90 (0.86-6.67)
Baseline attack rate of ≥2 attacks per month, n (%)[b]	85 (70%)
Median age at symptom onset (min, max)	11 (0.5, 55.0)
History of laryngeal attack, n (%)	90 (74%)
Use of past prophylactic treatment for HAE, n (%)[c]	91 (75%)
Any past prophylactic C1 esterase inhibitor (C1-INH) use, n (%)[d]	53 (44%)
Any past prophylactic androgen use, n (%)[e]	65 (54%)

[a]Baseline investigator-confirmed attack rate was defined as (total number of investigator-confirmed HAE attacks experienced in the period between screening and first date/time of study drug) x 28/(date of first dose – date of screening + 1).[8]
[b]Based on 120 subjects. One subject was randomized but did not receive study drug. As this subject did not receive drug, the subject had no baseline calculations.[8]
[c]Responses for individual drugs may not be mutually exclusive. Percentages were based on the number of responses per category and may not sum to 100%.[8]
[d]Includes plasma-derived C1-INH replacement, recombinant C1-INH replacement, and fresh frozen plasma.[8]
[e]Includes unspecified androgens, oxandrolone, methyl-testosterone, danazol, and stanozolol.[8]

SELECT IMPORTANT SAFETY INFORMATION

A reduced dosage of 110 mg taken orally once daily with food is recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C) and in patients taking chronically administered P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) inhibitors (eg, cyclosporine).

Please see Important Safety Information on page 13 and accompanying full Prescribing Information.

orladeyo®
(berotralstat) capsules 150 mg

ORLADEYO® offers significant attack rate reduction[1]

APeX-2 part 1 primary efficacy endpoint: HAE attack rate over 24 weeks[1,11]

- ORLADEYO demonstrated a significant attack rate reduction over 24 weeks[1,11,a]
  - Patients receiving ORLADEYO saw a reduction from 3.06 to 1.31 attacks per month
  - Patients receiving placebo saw a reduction from 2.91 to 2.35 attacks per month
  - ORLADEYO demonstrated a 44% reduction vs placebo (*P*<0.001)
- The effect of ORLADEYO in reducing attacks was seen within the first 4 weeks and maintained over 24 weeks[1]

[a]The percent reduction in attack rate was greater with ORLADEYO 150 mg relative to placebo regardless of attack rate during the run-in period.[1]

ORLADEYO reduced the need for rescue therapy[11]

In an ad hoc analysis of the first 24 weeks of treatment, patients treated with ORLADEYO 150 mg experienced a reduction in rescue medication use per 28 days vs placebo (nominal *P*<0.001).[11]

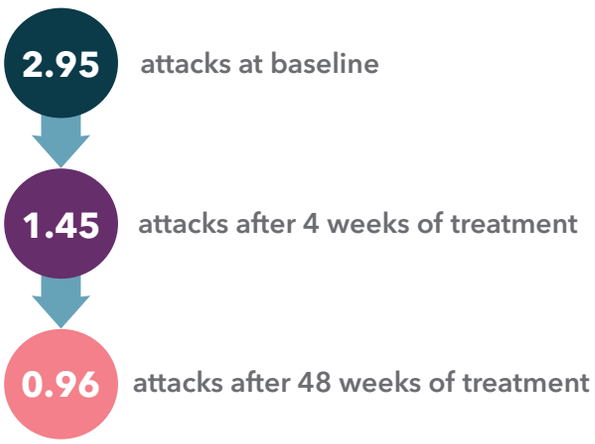
APeX-2 part 1 (0-24 weeks)

54%
REDUCTION IN RESCUE MEDICATION VS PLACEBO[11]

Results with ORLADEYO seen in APeX-2 part 1 continued into part 2[8,12]

Of the 31 patients who were randomized to ORLADEYO 150 mg at the beginning of APeX-2 and completed 48 weeks of treatment, the mean attack rate per 4 weeks declined from baseline to 48 weeks of treatment with ORLADEYO[8,12]:

APeX-2 parts 1-2 (0-48 weeks)



Every individual with HAE responds differently to treatment. The clinical phenotype is variable and does not predict response to prophylactic therapy.[4,5]

SELECT IMPORTANT SAFETY INFORMATION

Berotralstat is a substrate of P-gp and BCRP. P-gp inducers (eg, 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.

Please see Important Safety Information on page 13 and accompanying full Prescribing Information.

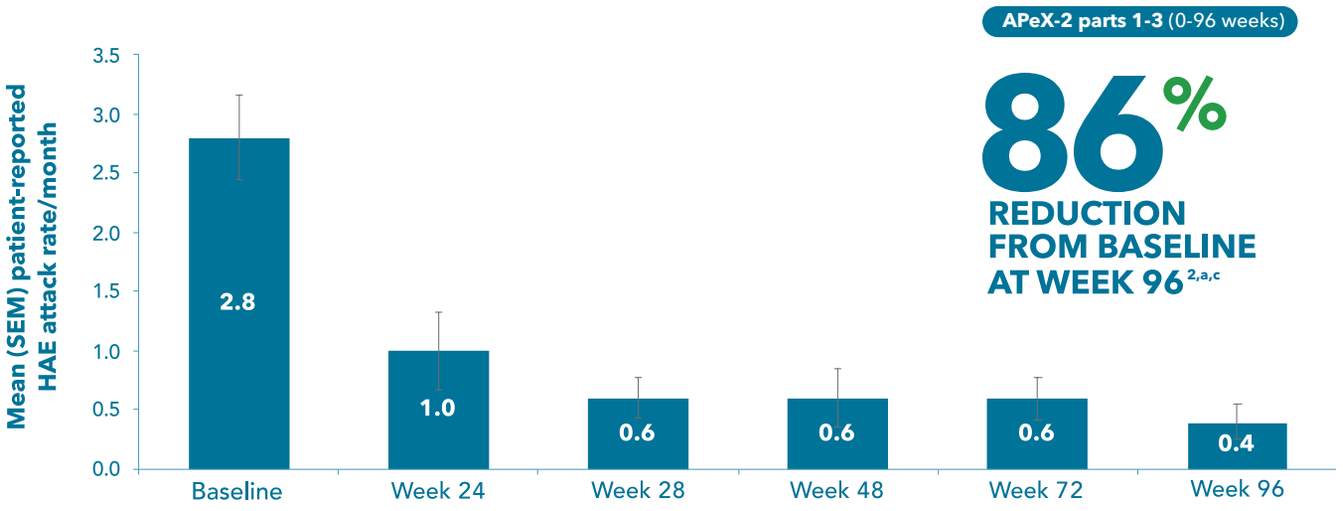
orladeyo®
(berotralstat) capsules 150 mg

ORLADEYO® provides sustained HAE attack rate reduction[2]

HAE attack rate reductions were seen within 4 weeks of starting ORLADEYO and were maintained over 96 weeks[1,2]

- Twenty-one patients who were randomized to ORLADEYO 150 mg at the beginning of APeX-2 and completed 96 weeks of treatment demonstrated a decline in mean attack rate per 4 weeks from baseline to 96 weeks of treatment[2,a]

HAE attack rate[b] per month[2]



Abbreviation: SEM, standard error of the mean.

[a]This reflects an ad hoc analysis of interim data.[8]

[b]Due to study design, investigator-confirmed attack rates were reported only during the first 48 weeks, while patient-reported attack rates were reported during weeks 49 to 96. For consistency across the entire 96 weeks, only patient-reported attack rates are reported. For analysis purposes, 1 month was defined as 4 weeks of treatment.[2]

[c]86% attack rate reduction from baseline to week 96 was seen for patients who completed 96 weeks of treatment with ORLADEYO 150 mg (n=21).[2]

In 16 of the last 17 months of treatment, median attack rate was 0 attacks per month.[2,a]

SELECT IMPORTANT SAFETY INFORMATION

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 or CYP3A4, appropriate monitoring and dose titration is recommended. ORLADEYO at a dose of 300 mg is a P-gp inhibitor. Appropriate monitoring and dose titration is recommended for P-gp substrates (eg, digoxin) when coadministering with ORLADEYO.

Please see Important Safety Information on page 13 and accompanying full Prescribing Information.

orladeyo®
(berotralstat) capsules 150 mg

The safety of ORLADEYO® is supported by data from patients across 2 clinical studies[1]

In APeX-2 part 1, the most common[a] treatment-emergent adverse reactions were abdominal pain, vomiting, diarrhea, back pain, and gastroesophageal reflux disease (GERD)[1]

Adverse reactions	Placebo (n=39)	ORLADEYO 110 mg (n=41)	ORLADEYO 150 mg (n=40)
	n (%)	n (%)	n (%)
Abdominal pain[b]	4 (10)	4 (10)	9 (23)
Vomiting	1 (3)	4 (10)	6 (15)
Diarrhea[c]	0	4 (10)	6 (15)
Back pain	1 (3)	1 (2)	4 (10)
GERD	0	4 (10)	2 (5)

[a] ≥10% and higher than placebo.[1]
[b] Includes abdominal pain, abdominal discomfort, abdominal tenderness, and upper abdominal pain.[1]
[c] Includes diarrhea and frequent bowel movements.[1]

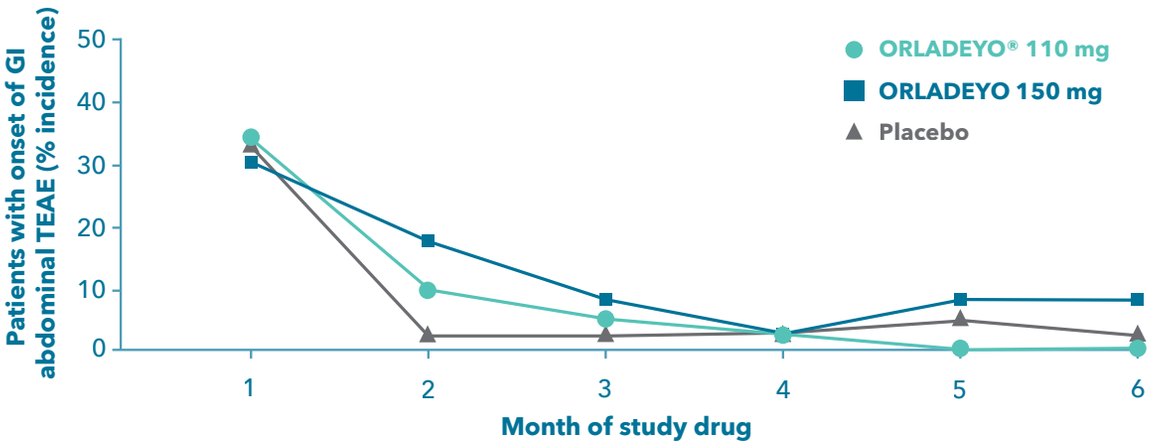
- No patients in the ORLADEYO 150 mg dose group and 1 patient in the ORLADEYO 110 mg dose group discontinued treatment due to a gastrointestinal (GI) adverse reaction in APeX-2 part 1[1]
- Findings from the open-label, long-term safety study, APeX-S (interim safety population, n=227), support the data observed in APeX-2 part 1[1]
- No new types of side effect were seen in those who continued ORLADEYO for 96 weeks[2]
  - One patient receiving ORLADEYO 150 mg discontinued treatment due to a GI abdominal adverse reaction in APeX-2 part 3[2]

Please see Important Safety Information on page 13 and accompanying full Prescribing Information.

orladeyo®
(berotralstat) capsules 150 mg

GI adverse reactions generally occurred early after initiation of treatment, became less frequent with time, and typically self-resolved[1]

Patients with new-onset GI abdominal TEAEs over time[13]



Patients on study drug:						
ORLADEYO 110 mg	41	41	41	41	40	38
ORLADEYO 150 mg	40	40	37	37	37	37
Placebo	39	39	38	37	36	34

Abbreviation: TEAE, treatment-emergent adverse event.

- If GI reactions persist, a reduced dosage of 110 mg once daily with food may be considered[1]

Setting expectations with patients regarding possible adverse reactions can help ensure a strong start.[7]

Please see Important Safety Information on page 13 and accompanying full Prescribing Information.

orladeyo®
(berotralstat) capsules 150 mg

ORLADEYO® patient retention[14]

Since approval, more than 2000 prescriptions have been written[14]

- Almost half of patients currently on ORLADEYO were previously taking another prophylactic therapy, including injectable prophylaxis[14,a]

More than 75% of patients who started on ORLADEYO **remained on therapy** for 6 months or longer[14,a]

[a]Data current as of February 2023.[14]

It's important to set expectations with patients starting ORLADEYO

- The recommended dosage of ORLADEYO is one 150 mg capsule taken orally once daily with food[1]
- Ensure patients have rescue therapy available for treatment of breakthrough HAE attacks[1]
- Steady state of ORLADEYO is reached in 6 to 12 days, but it may take longer for patients to experience benefit[1,11]
  - Encourage patients to check in frequently during the first few weeks of treatment[4]

Many patients are starting—and staying on—ORLADEYO, including those who were previously on injectable prophylaxis.[14,a]

SELECT IMPORTANT SAFETY INFORMATION

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

Please see Important Safety Information on page 13 and accompanying full Prescribing Information.

orladeyo®
(berotralstat) capsules 150 mg

Get your patients started with ORLADEYO®

Switching patients should be based on their clinical condition and your discretion[4]

Considerations for patients switching from other prophylactic treatments[8]	
C1-INH	Discontinue existing C1-INH dosing schedule 14 days after first dose of ORLADEYO.[a]
Lanadelumab-flyo	Day 1 of ORLADEYO dosing to occur on same day as lanadelumab injection. No further dosing of lanadelumab is required after initiating ORLADEYO.[a]
Androgens	BioCryst does not recommend the abrupt discontinuation of androgens.

[a]These recommendations are from the manufacturer of ORLADEYO and are based on clinical trial protocol. They have not been evaluated in a controlled clinical study.[8]

>80%
ATTACK-FREE MONTHS

Patients who switched to ORLADEYO from lanadelumab or subcutaneous C1-INH remained **attack-free >80%** of the months after switching[15,c]

- The transition from C1-INH or lanadelumab long-term prophylaxis to monotherapy with ORLADEYO was not associated with additional safety signals[15,c]

[c]These data are from an analysis of 34 US patients who switched as per the investigator's discretion from an injectable prophylaxis to ORLADEYO (treatment duration, 4 to 12 months) during a long-term safety study (APeX-S). It is unknown what these patients would have experienced had they remained on injectable prophylaxis.[15]

SELECT IMPORTANT SAFETY INFORMATION

There are insufficient data available to inform drug-related risks with ORLADEYO use in pregnancy. There are no data on the presence of berotralstat in human milk, its effects on the breastfed infant, or its effects on milk production.

Please see Important Safety Information on page 13 and accompanying full Prescribing Information.

orladeyo®
(berotralstat) capsules 150 mg

EMPOWER PATIENT SERVICES

One stop for all of your ORLADEYO® needs[8]

In a qualitative research study of patients who have experience with Empower Patient Services, nearly everyone rated it 10 out of 10 for excellence[8,a]

Empower Patient Services is known for customer service and a care team that truly cares. From copay assistance to ORLADEYO shipment coordination—your dedicated care team will be your resource for everything, including

Rapid therapy initiation

- Quick Start program provides access to ORLADEYO during insurance approval process for all insured patients[b]
- On average, patients receive their first shipment of ORLADEYO **in less than a week** following submission of the prescription

Comprehensive financial support

- Understanding benefits and insurance approval process
- Reimbursement and financial assistance for all patients, regardless of insurance status
- $0 copay for eligible commercially insured patients (up to the annual program maximum to cover out-of-pocket expenses per calendar year)[c]

Personalized HAE and ORLADEYO support

- Single point of contact for you and your patients
- Customized support during transition to ORLADEYO
- Coordination of deliveries
- Ongoing patient support

Give us a call at 1-866-5-EMPOWER (1-866-536-7693) or visit EmpowerORLADEYOhcp.com to learn more about the unique Empower Patient Services experience.

[a] This information was collected and analyzed using a qualitative methodology and a small sample size (N=15). As with all qualitative research, caution should be taken when interpreting these findings.[8]

[b] 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.

[c] Subject to terms and conditions of the Co-pay Assistance Program which your patients can obtain from their Empower Patient Services team. BioCryst reserves the right to rescind, revoke, or amend the program at any time without notice.

Please see Important Safety Information on page 13 and accompanying full Prescribing Information.

orladeyo®
(berotralstat) capsules 150 mg

Important Safety Information

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.

IMPORTANT SAFETY INFORMATION

An increase in QT prolongation was observed at dosages higher than the recommended 150 mg once-daily dosage and was concentration dependent.

The most common adverse reactions (≥10% and higher than placebo) in patients receiving ORLADEYO were abdominal pain, vomiting, diarrhea, back pain, and gastroesophageal reflux disease.

A reduced dosage of 110 mg taken orally once daily with food is recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C) and in patients taking chronically administered P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) inhibitors (eg, cyclosporine).

Berotralstat is a substrate of P-gp and BCRP. P-gp inducers (eg, 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.

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 or CYP3A4, appropriate monitoring and dose titration is recommended. ORLADEYO at a dose of 300 mg is a P-gp inhibitor. Appropriate monitoring and dose titration is recommended for P-gp substrates (eg, digoxin) when coadministering with ORLADEYO.

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

There are insufficient data available to inform drug-related risks with ORLADEYO use in pregnancy. There are no data on the presence of berotralstat in human milk, its effects on the breastfed infant, or its effects on milk production.

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.

For more information, please see the accompanying full Prescribing Information.

One capsule, once per day—this is ORLADEYO®[1]

Easy administration

- ORLADEYO is the first and only targeted oral prophylactic therapy for HAE, selectively binding to and inhibiting plasma kallikrein[1]
- ORLADEYO is a capsule taken once daily with food[1]

Sustained attack prevention

- 44% attack rate reduction vs placebo[1,11,a]
- 50% of patients achieved ≥70% attack rate reduction[11,b]
- 54% reduction in rescue medication use vs placebo[11,c]
- 86% attack rate reduction from baseline at week 96[2,d]

Established safety

- ORLADEYO is generally well-tolerated, with long-term safety data and experience[1,2]
- In APeX-2 part 1, the most common (≥10% and higher than placebo) treatment-emergent adverse reactions were abdominal pain, vomiting, diarrhea, back pain, and GERD[1]
- ORLADEYO should not be used for the treatment of acute HAE attacks[1]

1:1 support

- Your dedicated Empower Patient Services care team will serve as the single point of contact for you and your patients throughout the ORLADEYO journey

There is a strong demand for an oral prophylactic therapy[6]—talk to your patients about adding ORLADEYO to their treatment plan.

[a]APeX-2 part 1 primary efficacy endpoint; $P<0.001$.[1]
[b]From baseline to week 24, ad hoc analysis; nominal $P=0.002$.[1,11]
[c]Ad hoc analysis; nominal $P<0.001$.[8,11]
[d]From an ad hoc interim analysis of patients who completed 96 weeks of treatment with ORLADEYO 150 mg (n=21).[2]

SELECT IMPORTANT SAFETY INFORMATION

An increase in QT prolongation was observed at dosages higher than the recommended 150 mg once-daily dosage and was concentration dependent.

Please see Important Safety Information on page 13 and accompanying full Prescribing Information.

References: **1.** ORLADEYO [prescribing information]. Durham, NC: BioCryst Pharmaceuticals Inc.; 2022. **2.** Kiani S, Jacobs J, Desai B, et al. Durable reduction in hereditary angioedema (HAE) attack rates with berotralstat over 24 months: results from the phase 3 APeX-2 study. Presented at: European Academy of Allergy and Clinical Immunology Hybrid Congress; July 10-12, 2021; Madrid, Spain and Krakow, Poland. **3.** Radojicic, C, Riedl MA, Craig TJ, et al. Patient perspectives on the treatment burden of injectable medication for hereditary angioedema. *Allergy Asthma Proc.* 2021;42(3):S4-S10. doi:10.2500/aap.2021.42.210025. **4.** Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. *J Allergy Clin Immunol Pract.* 2021;9(1):132-150.e3. doi:10.1016/j.jaip.2020.08.046. **5.** Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema—the 2017 revision and update. *Allergy.* 2018;73(8):1575-1596. doi:10.1111/all.13384. **6.** Geba D, Sani JM, Gascon M, Hahn R, Aggarwal K, Rosselli J. Hereditary angioedema patients would prefer newer-generation oral prophylaxis. *J Drug Assess.* 2021;10(1):51-56. doi:10.1080/21556660.2020.1863699. **7.** Banerji A, Anderson J, Johnston DT. Optimal management of hereditary angioedema: shared decision-making. *J Asthma Allergy.* 2021;14:119-125. doi:10.2147/JAA.S284029. **8.** Data on file, BioCryst Pharmaceuticals Inc. **9.** Busse PJ, Christiansen SC. Hereditary angioedema. *N Engl J Med.* 2020;382(12):1136-1148. doi:10.1056/NEJMra1808012. **10.** Kaplan AP, Joseph K. The bradykinin-forming cascade and its role in hereditary angioedema. *Ann Allergy Asthma Immunol.* 2010;104(3):193-204. doi:10.1016/j.anai.2010.01.007. **11.** Zuraw B, Lumry WR, Johnston DT, et al. Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: a randomized, double-blind, placebo-controlled phase 3 trial. *J Allergy Clin Immunol.* 2021;148(1):164-172.e9. doi:10.1016/j.jaci.2020.10.015. **12.** Wedner HJ, Aygören-Pürsün E, Bernstein J, et al. Randomized trial of the efficacy and safety of berotralstat (BCX7353) as an oral prophylactic therapy for hereditary angioedema: results of APeX-2 through 48 weeks (part 2). *J Allergy Clin Immunol Pract.* 2021;9(6):2305-2314.e4. doi:10.1016/j.jaip.2021.03.057. **13.** Johnston D, Lumry WR, Banerji A, et al. Gastrointestinal adverse events observed with berotralstat (BCX7353) treatment for hereditary angioedema are primarily mild, self-limited, and diminish with time on treatment. Poster presented at: American Academy of Allergy, Asthma and Immunology Annual Meeting; March 13-16, 2020; Philadelphia, PA. **14.** Data on file from BioCryst Pharmaceuticals, Inc. third-party specialty pharmacy partner. **15.** Riedl MA, Sheridan WP, Noble LJ, Tomita D, Soteres D; APeX-S Study Investigators. Berotralstat demonstrates low hereditary angioedema (HAE) attack rates in patients switching from injectable prophylaxis. Poster presented at: American College of Allergy, Asthma and Immunology Annual Meeting; November 4-8, 2021; New Orleans, LA.

orladeyo® (berotralstat) capsules 150 mg

BioCryst®

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)].*

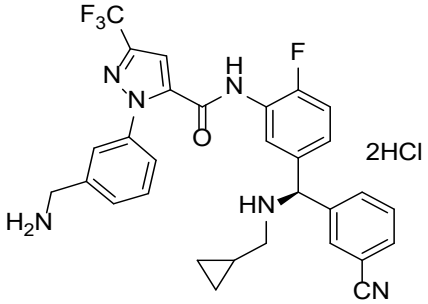
8.7 Hepatic Impairment

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)]*.

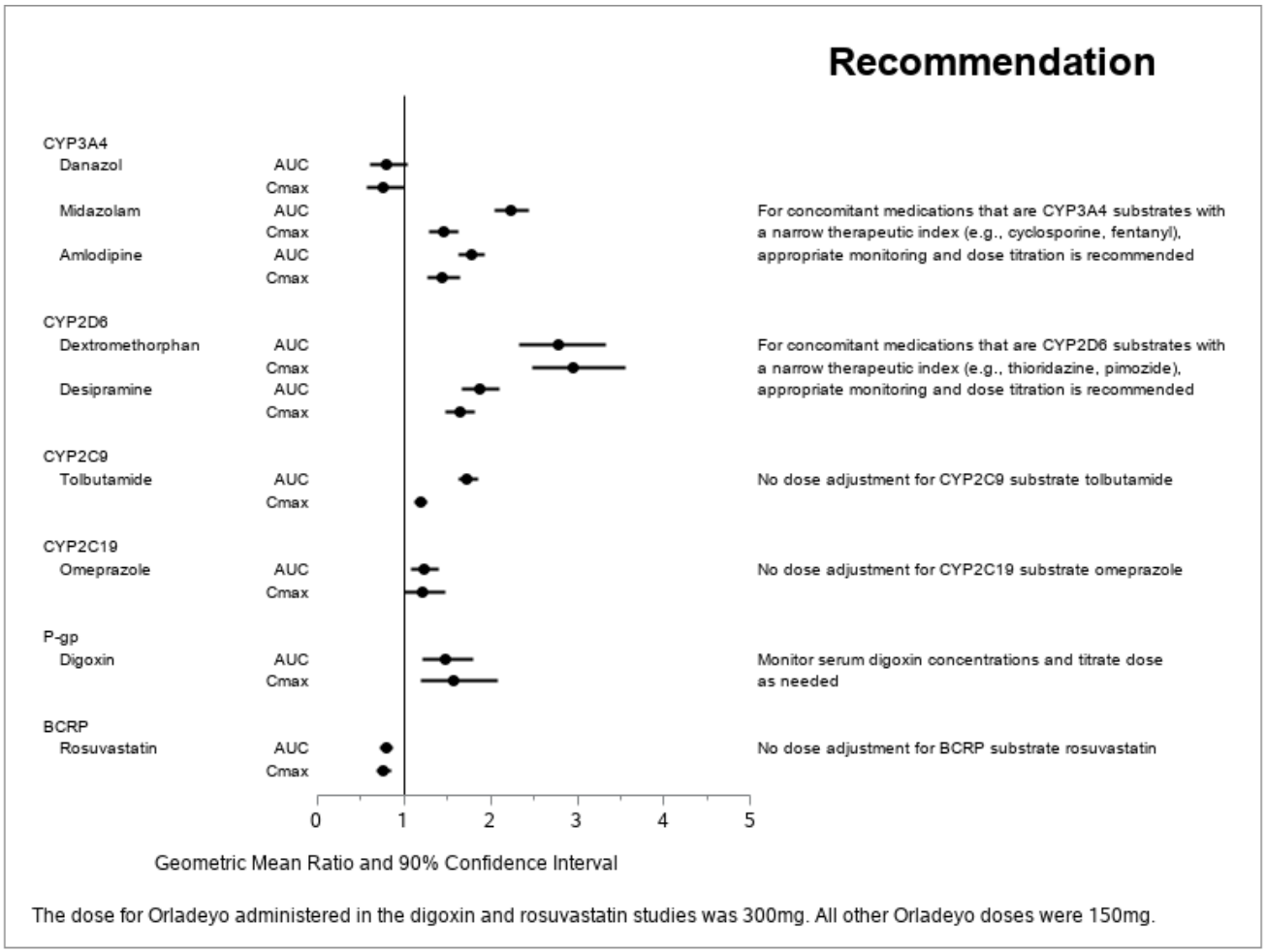
Effect of ORLADEYO on the Pharmacokinetics of Other Drugs

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	-

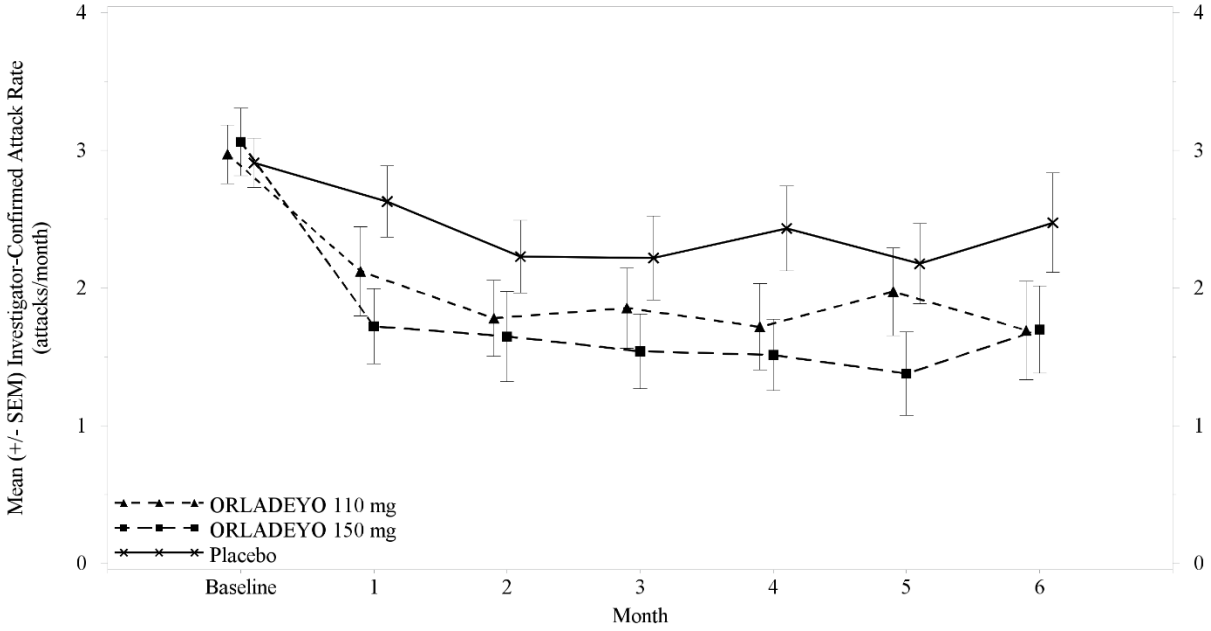
* One patient in the ITT analysis was randomized to placebo but was not treated.

† 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

ORLADEYO® is a registered trademark of BioCryst Pharmaceuticals, Inc.

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

214094-BC-001