For hereditary angioedema (HAE),

This is big.

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 12 and accompanying full Prescribing Information.

orladeyo®
(berotralstat) capsules 150 mg

biocryst®

Patients may be quietly coping with treatment burden

Self-administration challenges, needle fatigue, and other issues may be weighing patients with HAE down[1,2]

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.[2]

Talk to your patients about their satisfaction with their current therapy; prophylactic therapy should be individualized based on considerations such as[3,4]

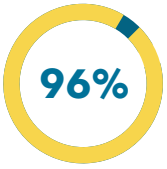
- Disease-related factors (physical, emotional, quality of life)
- Treatment-related factors (route of administration, side effects, availability/supply)
- Patient preference

Through shared decision making, patients are empowered to play a more active role in treatment decisions and be more compliant with their treatment, leading to better overall outcomes.[5]

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[7]

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[7]



of the 48 patients on a prophylactic therapy agree that an **oral prophylactic therapy would better fit their lives** vs an injectable HAE medication[7]

orladeyo®
(berotralstat) capsules 150 mg

ORLADEYO®: one capsule once per day[8]

ORLADEYO is the first and only targeted oral prophylactic therapy for HAE[8]

ORLADEYO offers simple and straightforward dosing and administration.[8]

- ORLADEYO is a single 150 mg[a] capsule taken every day with food[8]

Oral administration

No need for injection, infusion, or related supplies[8]

Flexibility

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

Easy storage

Room temperature; no refrigeration required[8]

ORLADEYO offers the consistency of daily dosing with the simplicity of oral administration.[8]

[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).[8]

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.

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orladeyo®
(berotralstat) capsules 150 mg

ORLADEYO® was studied in one of the largest clinical studies for a prophylactic therapy in HAE[2,6]

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

Participants[6]	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[2,6]	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[2,6]	Berotralstat 150 mg, berotralstat 110 mg, or placebo	Berotralstat 150 mg or berotralstat 110 mg	Berotralstat 150 mg

APeX-2 part 1 primary efficacy endpoint: HAE attack rate at 24 weeks[6]

[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.[6]

[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.[6]

ORLADEYO selectively binds and inhibits plasma kallikrein.[8]

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.

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(berotralstat) capsules 150 mg

ORLADEYO® was studied in patients like yours[2]

Patients in APeX-2 had a considerable disease history and burden[2]

Demographics and baseline characteristics of ITT population (N=121)[2]	
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-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).[2]
[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.[2]
[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%.[2]
[d]Includes plasma-derived C1-INH replacement, recombinant C1-INH replacement, and fresh frozen plasma.[2]
[e]Includes unspecified androgens, oxandrolone, methyl-testosterone, danazol, and stanozolol.[2]

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 12 and accompanying full Prescribing Information.

orladeyo®
(berotralstat) capsules 150 mg

ORLADEYO® offers significant attack rate reduction[8]

ORLADEYO demonstrated a significant attack rate reduction over 24 weeks from 3.06 to 1.31 attacks per month compared with a reduction of 2.91 to 2.35 attacks per month with placebo (44% reduction vs placebo, $P<0.001$).[6,8,a]

- The effect of ORLADEYO in reducing attacks was seen within the first 4 weeks and maintained over 24 weeks[8]

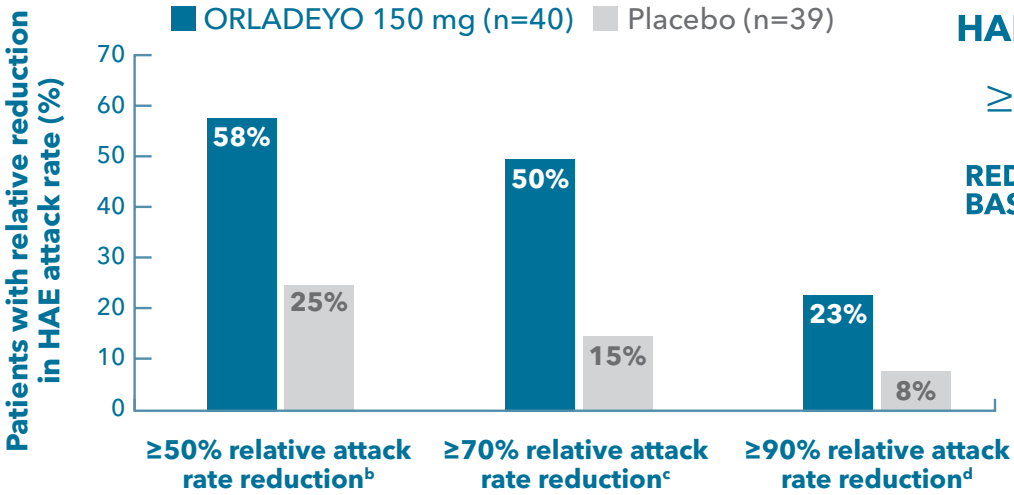
ORLADEYO reduced the need for rescue therapy[2]

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 $P<0.001$).[2]

54%
REDUCTION IN RESCUE MEDICATION VS PLACEBO

ORLADEYO consistently showed greater attack rate reductions compared with placebo across response thresholds[6]

Relative attack rate reduction from baseline to week 24[6]



HALF OF PATIENTS EXPERIENCED A **≥70%** **REDUCTION FROM BASELINE IN ATTACK RATE**

[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.[8]

[b] Exploratory endpoint; nominal $P=0.005$.[2,8]
[c] Ad hoc analysis; nominal $P=0.002$.[2,8]
[d] Ad hoc analysis; nominal $P=0.073$.[2,8]

Every individual with HAE responds differently to treatment. The clinical phenotype is variable and does not predict response to prophylactic therapy.[3,4]

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 12 and accompanying full Prescribing Information.

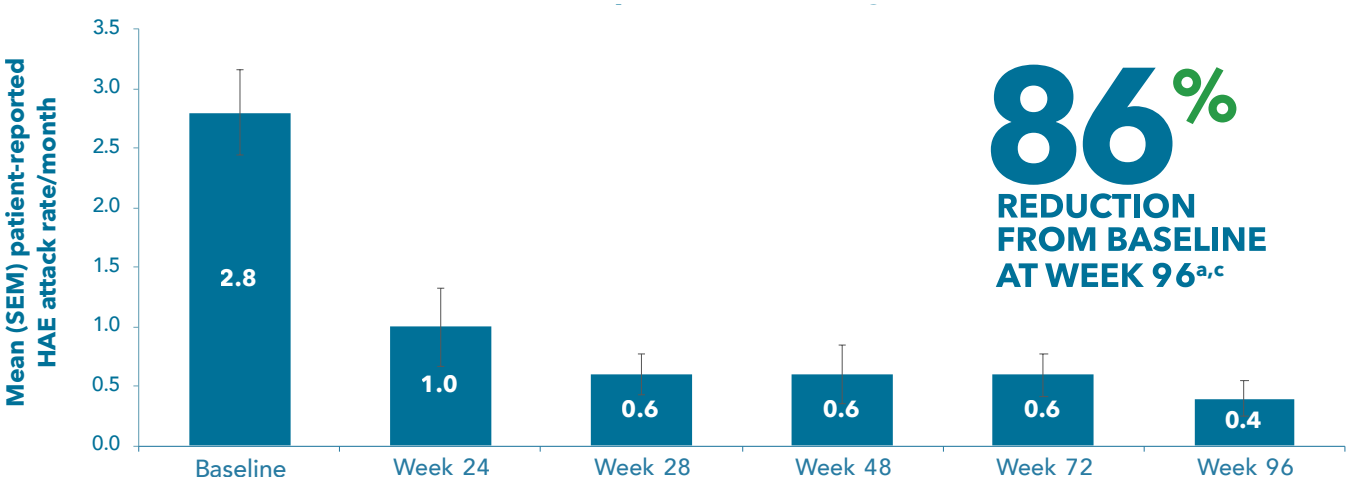
orladeyo®
(berotralstat) capsules 150 mg

ORLADEYO® provides sustained HAE attack rate reduction[9]

Patients who completed 96 weeks of treatment saw sustained reductions in their HAE attack rates, demonstrating the durability of ORLADEYO[9]

- 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[9,a]

HAE attack rate[b] per month through week 96[9]



Abbreviation: SEM, standard error of the mean.

[a] This reflects an ad hoc analysis of interim data.[2]

[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.[9]

[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).[9]

In 16 of the last 17 months of treatment, median attack rate was 0 attacks per month.[9,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 12 and accompanying full Prescribing Information.

orladeyo®
(berotralstat) capsules 150 mg

ORLADEYO® was studied in an open-label, nonrandomized, long-term safety study[10]

With the addition of APeX-S, ORLADEYO has been studied in one of the largest clinical study programs for HAE[2,6]

Participants[2,10]	An interim safety population of 227 patients (≥12 years of age) with confirmed HAE type 1 or 2
Long-term open-label[10]	103 patients completed 48 weeks of treatment at the time of the interim analysis
Daily dosing regimen[10]	Berotralstat 150 mg or berotralstat 110 mg

APeX-S objectives

- Primary objective: long-term safety and tolerability of daily dosing of ORLADEYO[10]
- Secondary objective: effectiveness of ORLADEYO during long-term administration[10]

Long-term effectiveness data from APeX-S are consistent with durability data from APeX-2[10]

The first 73 patients in the ORLADEYO 150 mg group to complete 48 weeks of treatment experienced a mean attack rate per 4 weeks of[2,10]

In 5 of the last 6 months of treatment, median attack rate was 0 attacks per month.[10,a]

[a]In an ad hoc analysis of those who had completed 48 weeks of the ongoing study.[10]

SELECT IMPORTANT SAFETY INFORMATION

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.

Please see Important Safety Information on page 12 and accompanying full Prescribing Information.

orladeyo®
(berotralstat) capsules 150 mg

The safety of ORLADEYO® is supported by data from patients across 2 clinical studies[8]

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)[8]

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.[8]
[b] Includes abdominal pain, abdominal discomfort, abdominal tenderness, and upper abdominal pain.[8]
[c] Includes diarrhea and frequent bowel movements.[8]

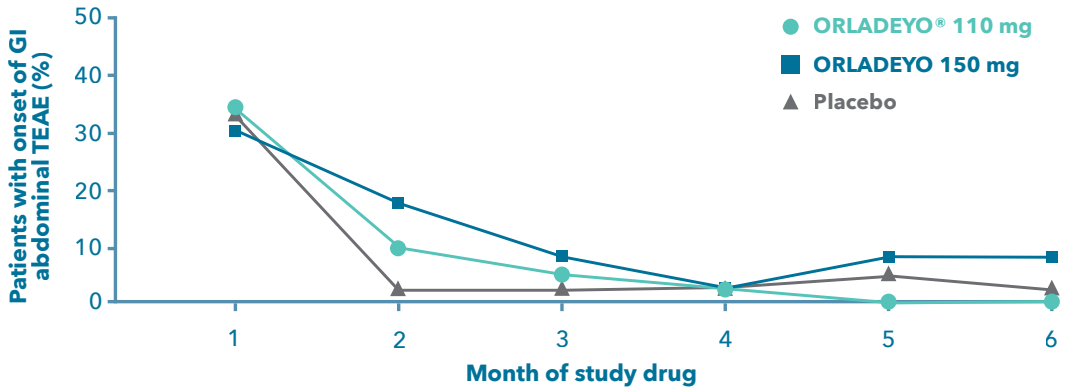
- If gastrointestinal (GI) reactions persist, a reduced dosage of 110 mg once daily with food may be considered[8]
- No patients in the ORLADEYO 150 mg dose group and 1 patient in the ORLADEYO 110 mg dose group discontinued treatment due to a GI adverse reaction in APeX-2 part 1[8]

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).[2,8]

Please see Important Safety Information on page 12 and accompanying full Prescribing Information.

GI adverse reactions generally occurred early after initiation of treatment, became less frequent with time, and typically self-resolved[8]

Incidence of new-onset GI abdominal TEAEs by month[11]



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.

Most common[a] adverse reactions in APeX-2 parts 1 and 2 or part 3[9]

Adverse reactions[b]	Up to 48 weeks of exposure (parts 1 and 2) n (%)	>48 to 96 weeks of exposure (part 3) n (%)
Nasopharyngitis	11 (42)	7 (27)
Upper respiratory tract infection	4 (15)	1 (4)
Sinusitis	3 (12)	1 (4)
Nausea	6 (23)	0
Vomiting	5 (19)	0
Abdominal pain	4 (15)	2 (8)
Diarrhea	4 (15)	2 (8)
Abdominal discomfort	4 (15)	1 (4)
Dyspepsia	4 (15)	0
Abdominal pain upper	3 (12)	0
Back pain	3 (12)	0
Headache	5 (19)	0
Fatigue	3 (12)	0

- One patient receiving ORLADEYO 150 mg discontinued treatment due to GI abdominal adverse reactions in APeX-2 part 3[9]

[a] ≥10% of patients for APeX-2 part 1 and 2 or part 3.[9]
[b] From an ad hoc, interim analysis of 26 patients who finished 48 weeks of treatment and entered APeX-2 part 3.[9]

Please see Important Safety Information on page 12 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[2]

Considerations based on clinical trial protocol[2]	
C1 esterase inhibitor C1-INH	Discontinue existing C1-INH dosing schedule 14 days after first dose of ORLADEYO.
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.

These recommendations are from the manufacturer of ORLADEYO and have not been evaluated in a controlled clinical study

Dosing recommendations

- The recommended dosage of ORLADEYO is one 150 mg capsule taken orally once daily with food[8]
- For patients with moderate or severe hepatic impairment (Child-Pugh B or C) and patients with chronic administration of P-glycoprotein or breast cancer–resistant protein inhibitors (eg, cyclosporine), the recommended dosage is one 110 mg capsule taken orally once daily with food[8]

Other considerations

- Ensure patients have rescue therapy available for treatment of breakthrough HAE attacks[8]
- Patients should not take additional doses of ORLADEYO to treat an acute attack of HAE; the safety and effectiveness of ORLADEYO as a rescue treatment for HAE attacks have not been established[8]
- Additional doses or dosages of ORLADEYO higher than 150 mg once daily are not recommended due to the potential for QT prolongation[8]
- GI reactions may occur in patients receiving ORLADEYO. If GI reactions persist, a reduced dosage of 110 mg once daily with food may be considered[8]

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 12 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.

Please see accompanying full Prescribing Information.

orladeyo®
(berotralstat) capsules 150 mg

EMPOWER PATIENT SERVICES

One stop for all of your ORLADEYO® needs

Rapid therapy initiation

- Quick Start program provides access to ORLADEYO during insurance approval process for all insured patients[a]
- 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 commercially insured patients (up to $40,000 to cover out-of-pocket expenses per calendar year)[b]

Personalized HAE and ORLADEYO support

- 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] 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.

[b] Subject to terms and conditions of the copay assistance program. To read the full terms and conditions, visit www.ORLADEYOhcp.com/copayassistance. BioCryst reserves the right to rescind, revoke, or amend the program at any time without notice.

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ORLADEYO® is the first and only targeted oral therapy for HAE

Easy administration

ORLADEYO offers the consistency of daily dosing with the simplicity of oral administration[8]

Sustained attack prevention

ORLADEYO offers significant and sustained HAE attack rate reduction[8,9]

Established safety

The safety of ORLADEYO is supported by data from 2 clinical studies[2,8]

1:1 support

Patients receive personalized HAE and ORLADEYO support from Empower Patient Services

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 12 and accompanying full Prescribing Information.

References: **1.** Banerji A. The burden of illness in patients with hereditary angioedema. *Ann Allergy Asthma Immunol*. 2013;111(5):329-336. doi:10.1016/j.anai.2013.08.019. **2.** Data on file, BioCryst Pharmaceuticals Inc. **3.** 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. **4.** 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. **5.** 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. **6.** 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. **7.** 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. **8.** ORLADEYO [prescribing information]. Durham, NC: BioCryst Pharmaceuticals Inc.; 2020. **9.** 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. **10.** Farkas H, Stobiecki M, Peter J, et al. Long-term safety and effectiveness of berotralstat for hereditary angioedema: the open-label APeX-S study. *Clin Transl Allergy.* 2021;11(4):e12035. doi:10.1002/clt2.12035. **11.** 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.

orladeyo® (berotralstat) capsules 150 mg

BioCryst®