orladeyo

(berotralstat) capsules 150 mg

BioCryst Pharmaceuticals, Inc.

About ORLADEYO® (berotralstat)

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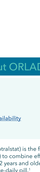
Capsule not actual size

ORLADEYO® (berotralstat) is the first and only targeted preventative therapy for hereditary angioedema (HAE) to combine effective attack prevention and oral administration in adult and pediatric patients 12 years and older. ORLADEYO provides proven, significant and sustained attack prevention in a once-daily pill.[1]



HAE is a rare, inherited disease characterized by repeated painful and unpredictable episodes (or attacks) of severe submucosal and/or subcutaneous swelling in various parts of the body.[1]

It affects about 1 in 50,000 people in the United States and, in most cases, is autosomal dominant, meaning children of a parent diagnosed with HAE have a 50% chance of inheriting the disorder.[2]

HAE Treatment and the Impact of an Oral Option

HAE consensus guidelines state that the overall goals of HAE treatment are to reduce morbidity and mortality, and to restore a normal quality of life to patients.[3]

The prevention options available to people with HAE can be divided into two categories and should be individualized based on a patient's lifestyle, medical needs and preferences:[3]

- **On-demand therapy** is provided for acute HAE attacks and focuses on reducing the severity and duration of an ongoing attack, with the goal of resolving symptoms as quickly as possible.
- **Regular dosing of preventative, or prophylactic, therapy** is designed to prevent attacks. The short-term goal of prophylactic therapy focuses on reducing the likelihood of swells in response to an anticipated traumatic event, like a medical procedure. Treatment with long-term prophylactic therapy, like ORLADEYO, focuses on reducing the number and severity of HAE attacks and associated burden of disease, and restoring normal quality of life. There are multiple routes of administration for preventative therapies, including intravenous, subcutaneous and oral.[3,4]
- **Some therapies can be burdensome.** For example, some intravenous therapies require injecting oneself up to 12 times per year for prophylaxis alone.[4] A recent study showed that most people living with HAE would prefer an oral, once-daily preventative option, even if an injectable option meant less frequent dosing, as long as they could expect similar effectiveness.[4]

ORLADEYO offers:

- **Easy administration**: One 150 mg capsule, once per day at the same time of day with food
- **Flexible dosing**: ORLADEYO can be taken anywhere
- **Convenient storage**: Room temperature; no refrigeration needed
- **Innovative design**: Not dependent on the availability of human plasma

*According to an online survey of 150 people aged ≥18 years living with HAE. Ninety-eight percent of respondents were receiving HAE treatment at the time of the survey. Dosing frequency did not significantly impact respondents' answers for preferring oral prophylaxis.

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SELECT IMPORTANT SAFETY INFORMATION

It is not known if ORLADEYO is safe and effective to treat an acute HAE attack, therefore ORLADEYO should not be used to treat an acute HAE attack. Do not take more than one capsule of ORLADEYO per day because extra doses can cause heart rhythm problems.

Please see Important Safety Information at the bottom and full Prescribing Information, including the Patient Information, at Orladeyo.com.

How ORLADEYO Works

One pill of ORLADEYO per day works to prevent HAE attacks by decreasing the activity of plasma kallikrein.

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

In HAE, uncontrolled plasma kallikrein activity triggers an overproduction of bradykinin, which leads to vasodilation, vascular leakage and subsequent swelling.[1,7]

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ORLADEYO Development and Availability

BioCryst discovered ORLADEYO® in 2013 and brought it to patients in just seven years - shorter than the typical diagnostic delay of around eight years for people with HAE.[8] ORLADEYO was approved by the U.S. Food and Drug Administration (FDA) and launched in the United States in December 2020, with many subsequent ex-U.S. approvals thereafter.

Major ORLADEYO Milestones:

2012	• BioCryst announced a focus on rare diseases, including HAE
2013	• Discovered ORLADEYO (then known as BCX7353) at the BioCryst Discovery Center of Excellence in Hoover, Ala.
2014	• Initiated Phase 2 APeX-1 clinical study
2018	• Received Fast Track Designation from FDA • New England Journal of Medicine published APeX-1 results • Initiated Phase 3 APeX-2 clinical study
2019	• Announced APeX-2 results • Submitted new drug application (NDA)
2020	• Received FDA approval and launched in the US.
TODAY	• In addition to the US, ORLADEYO is approved in multiple markets around the world: Japan[1], United Arab Emirates[9], Switzerland, Chile[1], Mexico[1], European Union[10], Canada, Saudi Arabia[1], Argentina[1], Peru[1], United Kingdom, Brazil[1]
	BioCryst commercializes ORLADEYO in partnership with Torii Pharmaceutical, Takeda BioPharma, NeuBiopharma, Neopharm Group, Yiel Pharma
	• BioCryst is evaluating an oral granule formulation of ORLADEYO in pediatric patients ages 2 to <12 years in the APeX-P pivotal study
2025 (est)	• Regulatory submission planned for pediatric indication

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Before taking ORLADEYO, tell your healthcare provider about all of your medical conditions, including if you:

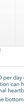
- have liver problems or are on kidney dialysis;
- are pregnant or planning to become pregnant. It is not known if ORLADEYO can harm your unborn baby;
- are breastfeeding or plan to breastfeed. It is not known if ORLADEYO passes into your breastmilk. Talk to your healthcare provider about the best way to feed your baby while taking ORLADEYO.

Please see Important Safety Information at the bottom and full Prescribing Information, including the Patient Information, at Orladeyo.com.

Patient Impact and Access

>2.5K

PATIENTS PRESCRIBED ORLADEYO* SINCE DECEMBER 2020[1]



~200

ANTICIPATED NET NEW PATIENTS EACH YEAR FOR THE NEXT FEW YEARS

EMPOWER

BioCryst's Empower Patient Services offers a single pharmacy provider with a dedicated team of seasoned experts who provide individualized and streamlined support navigating the insurance process, affordability, adherence and related needs throughout the ORLADEYO journey.

*as of 4Q24

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Current and Peak Sales

ORLADEYO has generated $1.0 billion in global revenue since launch.**

$1B

PREDICTED

Sales trajectory is on track for $1B in peak global sales, which takes into account current and projected future competition and ~2,000 patients total on active treatment with ORLADEYO.*

*as of 4Q24

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SELECT IMPORTANT SAFETY INFORMATION

Taking more than one capsule of ORLADEYO per day may cause serious side effects, including heart rhythm problems. A heart rhythm problem called QT prolongation can happen in people who take more than one capsule of ORLADEYO per day. This condition can cause an abnormal heartbeat. Do not take more than one capsule of ORLADEYO per day.

Please see Important Safety Information at the bottom and full Prescribing Information, including the Patient Information, at Orladeyo.com.

Clinical Data and Real-world Evidence

The safety and effectiveness of ORLADEYO has been evaluated in a robust clinical program - including the APeX-2 and APeX-2* studies - and its real-world clinical use has been analyzed as part of BioCryst's continued commitment to demonstrating the impact of ORLADEYO.

Highlights from Final Published Analysis of APeX-2 96-week Data[8,9,11]

- Patients who received ORLADEYO 150 mg in this long-term, three-part study (n=22) reported rapid and sustained improvements from baseline of 3.3 attacks per month to 0.3 attacks per month after two years.
- Patients who received ORLADEYO 150 mg from Day 1 and completed the study (n=21) experienced an average reduction in monthly attack rate of 90.8% compared to baseline.
- More than half of people had zero attacks in 17 of the last 18 months of treatment. The primary objective in Part 3 of the study was to evaluate long-term safety and tolerability.

Patients Experience Excellent HAE Control on ORLADEYO[9,10]

LONG-TERM CLINICAL EVIDENCE

90.8%

Attack reduction vs baseline after 96 weeks on ORLADEYO 150 mg in APeX-2

Source: Kern-Allman S, Cicero R, Craig T et al. Clinical-only and berotralstat for long-term prophylaxis of hereditary angioedema: The open-label extension of the APeX-2 randomized trial. J Allergy Clin Immunol December 2023

LONG-TERM REAL-WORLD EVIDENCE

RAPID
attack control regardless of baseline rate or C1-INH level and function

SUSTAINED
attack control regardless of baseline rate or C1-INH level and function

ZERO
median monthly attack rate on ORLADEYO for patients who were attack free at baseline

Source: AAAAI Annual Meeting 2024 Poster Presentations, February 2024

*APeX-2 was a 3-part Phase 3 study. Participants included 121 patients aged 12 years and older with confirmed HAE type 1 or 2 who experienced ≥2 moderate/severe treatment attacks during the 8 weeks run-in period. In APeX-2 Part 1, 40 Gen baseline endpoints were meaningfully improved in all study arms beyond the AUC WOD of 6; however, change in AE Gen. total scores from baseline to week 24 was not significant versus placebo.

Data Highlights

BioCryst has reported other long-term data and additional analyses from ORLADEYO clinical studies and real-world evidence, including:

CLINICAL RESULTS

- Results from Part 3 of APeX-2 published in JACI: In Practice showed clinically meaningful reductions in HAE attacks and improved quality of life[9] over 96 weeks of treatment with ORLADEYO.
- Final safety and effectiveness analysis from APeX-S showed ORLADEYO 150 mg resulted in a median attack rate of 0.0 attacks per month in 20 of 24 months (AAAAI 2023).[10]

Hypothesis testing and statistical analyses were not prespecified in the protocol for Part 3, and so such conclusions around the significance of changes from baseline cannot be made.

Ns 22 years of treatment with ORLADEYO 150 mg compared with baseline (n=19 patients); 2 patients did not receive any rescue medication at baseline).

REAL-WORLD EVIDENCE

- Real-world HEOR data showed reductions in healthcare resource utilization among U.S. patients following initiation of ORLADEYO (ISPOR 2024).[11]
- Real-world data showed patients who initiated ORLADEYO experienced rapid, substantial and sustained reductions in attack rates through 18 months of treatment regardless of the severity of their disease, their history of prior prophylaxis or their C1-inhibitor (C1-INH) level and function (AAAAI 2024).[12]
- Patients who self-reported HAE attack rates at baseline had a median attack rate of 0 attacks per month across a 12-month period (AAAAI 2023).[13]
- Patients remained attack free for 98% of days after switching from an injectable therapy to ORLADEYO (Annals of Allergy, Asthma & Immunology, 2024).[13]
- Patients who completed 96 weeks on ORLADEYO 150 mg in APeX-2 saw an 88% reduction in rescue medication use,[9] and had 95% attack-free days in Part 3 of the study.[9]

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Established Safety

The safety of ORLADEYO is supported by data from patients across two clinical studies and analyses of real-world outcomes.[1,11,14]

In APeX-2 Part 1, the most common* treatment-emergent adverse reactions (TEAEs) were abdominal pain, vomiting, diarrhea, back pain and gastroesophageal reflux disease (GERD). Gastrointestinal adverse reactions generally occurred early after initiation of treatment, became less frequent with time and typically self-resolved.

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

*n (%)

*≥10% and higher than placebo

† Includes abdominal pain, abdominal discomfort, abdominal tenderness and upper abdominal pain.[1]

‡ Includes diarrhea and frequent bowel movements.[1]

No patients in the ORLADEYO 150 mg dose group and one patient in the ORLADEYO 110 mg dose group discontinued treatment due to a GI adverse reaction in APeX-2 Part 1.[1]

Findings from the open-label, long-term safety study, APeX-S (final safety population, n=387), support the data observed in APeX-2 Part 1.[11,15]

No new safety signals were seen in those who continued ORLADEYO for 96 weeks. In APeX-2 Part 3 (n=81), the most common TEAEs were nasopharyngitis, urinary tract infection, abdominal pain, arthralgia, coronavirus infection and diarrhea. One patient receiving ORLADEYO 150 mg discontinued treatment due to a GI abdominal adverse reaction in APeX-2 Part 3.[11]

In APeX-S (n=387), the switch from lanadelumab to ORLADEYO was generally well tolerated. The most common adverse events (occurring in ≥5% of patients) were vomiting, diarrhea, upper respiratory tract infection, nausea, insomnia, pharyngitis, abdominal discomfort, back pain and dysmenorrhea. No patients in this analysis discontinued ORLADEYO due to an adverse event.[11]

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IMPORTANT SAFETY INFORMATION

What is ORLADEYO® (berotralstat)?

ORLADEYO (ior-lah-DAY-oh) is a prescription medicine used to prevent attacks of hereditary angioedema (HAE) in adults and children 12 years of age and older. It is not known if ORLADEYO is safe and effective in children under 12 years of age.

It is not known if ORLADEYO is safe and effective to treat an acute HAE attack, therefore ORLADEYO should not be used to treat an acute HAE attack.

Do not take more than one capsule of ORLADEYO per day because extra doses can cause heart rhythm problems.

Before taking ORLADEYO, tell your healthcare provider about all of your medical conditions, including if you

- have liver problems or are on kidney dialysis.
- are pregnant or planning to become pregnant. It is not known if ORLADEYO can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if ORLADEYO passes into your breastmilk. Talk to your healthcare provider about the best way to feed your baby while taking ORLADEYO.

Tell your healthcare provider about all of the medicines you take, including other medicines for HAE, prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking ORLADEYO with certain other medicines may affect the way other medicines work and other medicines may affect how ORLADEYO works.

Know the medicines you take and keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

What are the possible side effects of ORLADEYO?

Taking more than one capsule of ORLADEYO per day may cause serious side effects, including heart rhythm problems. A heart rhythm problem called QT prolongation can happen in people who take more than one capsule of ORLADEYO per day. This condition can cause an abnormal heartbeat. Do not take more than one capsule of ORLADEYO per day.

The most common side effects of ORLADEYO include abdominal pain, vomiting, diarrhea, back pain, and heartburn. These are not all the possible side effects of ORLADEYO. For more information, ask your healthcare provider or pharmacist.

Talk to your healthcare provider for medical advice about side effects.

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You are encouraged to report side effects of prescription drugs to BioCryst Pharmaceuticals, Inc at 1-833-223-2279 or to the FDA at www.fda.gov/medwatch or 1-800-FDA-1088.

References: 1. ORLADEYO [prescribing information]. Durham, NC: BioCryst Pharmaceuticals, Inc.; 2023. 2. Bernstein JA. Am J Manag Care. 2018;24(14 suppl):S392-S398. 3. Busse P, Christiansen SC, Riedl MA et al. J Allergy Clin Immunol Pract. 2021;9(1):132-150.e3. 4. Craig T, Bowen P, Grover RG, et al. Ann Allergy Asthma Immunol. 2018;121(6):673-679. 5. Cicardi M, Bork K, Caballero T, et al. Allergy. 2012;67(2):147-157. 6. Busse et al. N Engl J Med. 2020;382(1):136-148. 7. Kaplan et al. Ann Allergy Asthma Immunol. 2010;104(3):195-204. 8. HAE Diagnostic Website, BioCryst Pharmaceuticals Inc. 9. Data on File, BioCryst Pharmaceuticals Inc. 10. AAAAI Annual Meeting 2024 Poster Presentations February 2024. 11. Kern-Allman et al. J Allergy Clin Immunol Pract. 2024;12(3):733-743.e10. 12. Reguera-Ziralzo et al. Poster presented at: 2023 AAAAI Annual Meeting; February 24-27, 2023. 13. Riedl et al. Ann Allergy Asthma Immunol. 2024;132(4):505-511.e1. 14. Christiansen et al. Poster presented at: 2024 ISPOR Conference; May 5-8, 2024. 15. Davis-Lorton et al. Poster presented at: 2024 AAAAI Annual Meeting; February 23-26, 2024. 16. Wedner et al. Poster presented at: 2023 ACAAI Annual Meeting; November 9-13, 2023. 17. Aygören-Pürsün et al. Poster presented at: 2023 World Allergy Congress; December 1-5, 2023.

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