Orladeyo (berotralstat)

NEW PRODUCT SLIDESHOW

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Introduction

- **Brand name:** Orladeyo
- **Generic name:** Berotralstat
- **Pharmacologic class:** Plasma kallikrein inhibitor
- **Strength and Formulation:** 110mg, 150mg; capsules
- **Manufacturer:** BioCryst Pharmaceuticals
- **How supplied:** Caps—28
- **Legal Classification:** Rx

Orladeyo

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Indication

- Prophylaxis to prevent attacks of **hereditary angioedema (HAE)** in adults and pediatric patients 12 years and older.

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Limitations of Use

- Safety and effectiveness for treatment of acute HAE attacks: not established.
- Should not be used for treatment of acute HAE attacks.
- Additional doses or doses of Orladeyo higher than 150mg once daily are not recommended due to potential for QT prolongation.

Dosage and Administration

- ≥12yrs: 150mg once daily with food.
- Moderate or severe hepatic impairment (Child-Pugh B or C): 110mg once daily.
- Concomitant P-gp or BCRP inhibitors: 110mg once daily.
- Patients with persistent gastrointestinal reactions: consider a reduced dose of 110mg once daily.

Considerations for Special Populations

- **Pregnancy**: Insufficient data to inform drug-related risks.
- **Nursing mothers**: No data on presence of berotralstat in human milk; consider benefits of breastfeeding along with mother's clinical need and potential adverse effects.
- **Pediatric**: <12 years: not established.
- **Geriatrics**: Age does not have a clinically meaningful impact on systemic exposure.
- **Renal impairment**: ESRD (CrCl <15mL/min or eGFR <15mL/min/1.73m^2 or patients requiring hemodialysis): not recommended.
- **Hepatic impairment**: Moderate to severe hepatic impairment: reduce dose to 110mg once daily.

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Warnings and Precautions

- Additional doses or doses higher than 150mg once daily: not recommended.
- Increased risk of QT prolongation at doses higher than 150mg/day.

Interactions

- Concomitant use with P-gp or BCRP inhibitors (eg, cyclosporine); reduce dose of Orladeyo to 110mg once daily.
- May be antagonized by P-gp inducers (eg, rifampin, St. John’s wort); not recommended.
- Concomitant drugs with a narrow therapeutic index that are predominantly metabolized by CYP2D6 (eg, thioridazine, pimozide) or CYP3A4 (eg, cyclosporine, fentanyl); monitor and titrate dose.
- Concomitant use with P-gp substrates (eg, digoxin); monitor and titrate dose of substrate.

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Adverse Reactions

- **Most common (≥10%)**: Abdominal pain, vomiting, diarrhea, back pain, gastroesophageal reflux disease.
- **Other**: QT prolongation at doses higher than 150mg/day.

Mechanism of Action

- **Berotralstat** is a plasma kallikrein inhibitor that binds to plasma kallikrein and inhibits its proteolytic activity.
- By decreasing plasma kallikrein activity, berotralstat controls excess bradykinin generation in patients with HAE.

Pharmacokinetics

- **Absorption**: Median time to maximum plasma concentration is 5 hours (range: 1 to 8 hours).
- **Effect of food**: No differences in the C_{max} and AUC of berotralstat with a high-fat meal; however, the median T_{max} was delayed by 3 hours.
- **Plasma protein binding**: ~99%.
- **Metabolism**: CYP2D6 and CYP3A4.
- **Excretion**:
  - Median elimination half-life: ~93 hours (range: 39 to 152 hours).
  - Primarily excreted via fecal route; renal route is minor.

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Clinical Trials

- Approval based on Part 1 of a randomized, double-blind, placebo-controlled, parallel-group study (NCT3485911) for preventing angioedema attacks in 120 patients 12 years and older with Type I or II HAE.
- Patients were randomly assigned 1:1:1, stratified by baseline attack rate, to receive Orladeyo 110mg, 150mg, or placebo once daily with food for the 24-week treatment period (Part 1).
- Prior to entering the study, patients discontinued other prophylactic HAE medications, but all patients were allowed to use rescue medications for breakthrough attacks.

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Clinical Trials

- **Patient demographics**
  - 74% reported a history of laryngeal angioedema attacks.
  - 75% reported prior use of long-term prophylaxis.
  - Median attack rate during the prospective run-in period (baseline attack rate): 2.9 per month.
  - 70% had a baseline attack rate of ≥2 attacks per month.

Clinical Trials

- **Results at week 24**
  - Orladeyo 110mg reduced the rate of HAE attacks by 30% (95% CI, 4.6-48.7; *P* =.024) vs placebo.
  - Orladeyo 150mg reduced the rate of HAE attacks by 44.2% (95% CI, 23.0-59.5; *P* <.001) vs placebo.
  - The HAE attack rates per 28 days in the Orladeyo 110mg and 150mg arms were 1.65 and 1.31, respectively, vs 2.35 for placebo.

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Clinical Trials

- 58% of patients receiving Orladeyo 150mg and 51% of patients receiving Orladeyo 110mg had a ≥50% reduction in their HAE attack rates compared to baseline vs 25% of placebo patients.
- In post-hoc analyses, 50% and 23% of patients receiving Orladeyo 150mg, and 27% and 10% of patients receiving Orladeyo 110mg, had a ≥70% or ≥90% reduction in their HAE attack rates compared to baseline vs 15% and 8% of placebo patients, respectively.
- Orladeyo 110mg and 150mg reduced the rate of moderate or severe attacks by 10% and 40%, respectively, vs placebo.

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New Product Monograph

- For more information view the product monograph available at:

  https://www.empr.com/drug/orladeyo/