NEW DRUG APPROVAL

Brand Name	Orladeyo®
Generic Name	berotralstat
Drug Manufacturer	BioCryst Pharmaceuticals, Inc

New Drug Approval

FDA Approval Date: 12/03/2020

Review Designation: Standard; Orphan

Type of Review: Type 1 - New Molecular Entity

Dispensing Restriction: Specialty Only

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Hereditary angioedema (HAE) is an autosomal dominant disease caused by a deficiency in functional C1 inhibitor affecting an estimated 1 in 50,000 individuals in the United States. The disease is characterized by recurrent episodes of nonpruritic swelling of the hands, feet, arms, legs, trunk, face, genitalia, bowels, and larynx beginning in childhood or adolescence and continuing throughout the patient's lifetime. There is significant variability in both the severity and frequency of edema attacks. Untreated patients may suffer an attack as often as every few days, while patients undergoing prophylactic therapy may be symptom free for a decade or more.

Efficacy

Table 2. APeX-2 (NCT03485911): Study Design Summary

Study Population	• 120 participants (adults and adolescents ≥12 years of age) • Experienced at least 2 investigator-confirmed attacks within first 8 weeks of the run-in period and took at least one dose of study treatment
Interventions	• Randomized to berotralstat 110 mg, berotralstat 150 mg, or placebo for 24-week study period • Once daily with food • Patients discontinued other prophylactic HAE medications prior to study entry • Patients were allowed to use rescue medications for breakthrough attacks • 70% patients had baseline attack rate of ≥2 attacks/month
Endpoints	• **Primary endpoint:** reduction in HAE attack rate at 24 weeks
Efficacy Results	• **APeX-2 Results:** ○ Orladeyo 110 mg QD (n = 41): HAE attack rate 1.65, 30.0% reduction (*P* = 0.024) ○ Orladeyo 150 mg QD (n = 40): HAE attack rate 1.31, 44.2% reduction (*P* = 0.001) ○ Placebo (n = 40): HAE attack rate 2.35

Source: Orladeyo Prescribing Information

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Safety

ADVERSE EVENTS

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

WARNINGS & PRECAUTIONS

An increase in QT prolongation can occur at dosages higher than the recommended 150 mg once daily dosage. Additional doses or doses higher than 150 mg once daily are not recommended.

CONTRAINDICATIONS

None.

Clinical Pharmacology

MECHANISMS 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.

Dose & Administration

ADULTS

One capsule (150 mg) taken orally once daily with food.

PEDIATRICS

The safety and effectiveness in pediatric patients < 12 years of age have not been established. If age ≥ 12 years, refer to adult dosing.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

No dosage adjustment is recommended for patients with mild, moderate or severe renal impairment.

Has not been studied in those with End-Stage Renal Disease (CLCR < 15 mL/min or eGFR < 15 mL/min/1.73 m2 or patients requiring hemodialysis), and therefore is not recommended for use in these patient populations.

HEPATIC IMPAIRMENT

No dosage adjustment is recommended for patients with mild hepatic impairment (Child-Pugh Class A).

In patients with moderate or severe hepatic impairment (Child-Pugh B or C), the recommended dose is 110 mg once daily with food.

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Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Capsules: 150 mg, 110 mg