New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Orladeyo™ (berotralstat) [BioCryst Pharmaceuticals, Inc.]**
Dosage Formulations:	110 mg and 150 mg capsules
FDA Approval Date: **FDB File Date:**	FDA: December 3, 2020 FDB: December 13, 2020
Indication:	Prophylaxis to prevent attacks of hereditary angioedema (HAE) in adults and pediatric patients aged 12 years and older – not for acute treatment
Mechanism of Action:	• Orladeyo is a plasma kallikrein inhibitor that binds to plasma kallikrein and inhibits its activity to control excess bradykinin generation in patients with HAE. • 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 (C1INH) 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.

Dose/ Administration:	• Recommended: 150 mg once daily with food
	• Dose reduced to 110 mg once daily for:
	  ○ Patients with moderate to severe hepatic impairment (Child-Pugh B or C)
	  ○ Patients using concomitant P-gp or BCRP inhibitors (e.g., cyclosporine)
	  ○ Patients with persistent gastrointestinal reactions

Disease State Clinical Highlights:	• HAE is a rare, genetic, and potentially life-threatening disorder typically beginning in childhood or adolescence and continuing throughout the patient's lifetime.
	• HAE affects an estimated 1 in 50,000 people in the United States.
	• HAE is divided into 2 main types: HAE due to C1INH deficiency (HAE-C1INH) and HAE with normal C1INH (HAE-nl-C1INH)
	  ○ HAE-C1INH is further divided into 2 subtypes, both caused by mutations in the gene that encodes C1INH:
	  ▪ Type 1 HAE is characterized by deficient levels of C1INH protein and function
	  ▪ Type II HAE is characterized by normal levels of C1INH protein that is dysfunctional
	  ○ HAE-nl-C1INH, first described in 2000, is further divided into 5 subtypes:
	  ▪ HAE-FXII is due to mutations in F12, the gene encoding coagulation FXII
	  ▪ HAE-PLG is due to mutations in PLG, the gene encoding plasminogen
	  ▪ HAE-ANGPT1 is due to mutations in ANGPT1, the gene encoding angiopoietin-1
	  ▪ HAE-KNG1 is due to mutations in the kininogen 1 gene
	  ▪ HAE-U represents patients for whom the responsible mutation has not yet been defined
	• Symptoms include recurrent attacks of severe swelling of the skin and mucous membranes, typically in 3 areas of the body:
	  ○ Skin – most commonly in the face, hands, arms, legs, genitals, and buttocks potentially causing pain, dysfunction, or disfigurement, but generally temporary and not dangerous
	  ○ Gastrointestinal tract – may involve the stomach, intestines, bladder, or urethra causing nausea, vomiting, diarrhea, and pain
	  ○ Upper airway – may involve larynx and tongue, potentially leading to life-threatening upper airway obstruction
	• Severity and frequency of attacks can vary from person to person. Approximately 50% of individuals with untreated HAE have monthly exacerbations and another 40% have 6

to 11 attacks annually. Patients treated with prophylactic therapy may be attack free for 10 years or longer.

- Diagnosis of HAE should be considered in individuals with recurrent episodes of swelling, especially if the swelling is not responsive to antihistamines or steroids or is associated with hives. In hypersensitivity reactions, the main mediator of swelling is histamine; in HAE, the main mediator of swelling is bradykinin.
- Criteria for diagnosis of HAE:
  - HAE-C1INH:
    - Required:
      - History of recurrent angioedema in the absence of concomitant urticaria or medication known to cause angioedema
      - Low (< 50% of normal) C1INH antigenic or functional level
      - Low C4 level (either at baseline or during an attack)
    - Supportive:
      - Demonstration of a pathologic *SERPING1* variant
      - Family history of recurrent angioedema
      - Age of symptom onset < 40 years
  - HAE-nl-C1INH:
    - Required:
      - History of recurrent angioedema in the absence of concomitant urticaria or medication known to cause angioedema
      - Normal or near normal C4, C1INH antigen, and C1INH function
      - At least one of the following:
        - Demonstration of a pathogenic variant associated with the disease
        - Positive family history of recurrent angioedema and documented lack of efficacy of high-dose antihistamine therapy for at least 1 month or an interval expected to be associated with 3 or more attacks of angioedema, whichever is longer
    - Supportive (must have both):
      - History of rapid and durable response to a bradykinin-targeted medication
      - Predominant documented visible angioedema or evidence of bowel wall edema documented by CT or MRI in patients with predominant abdominal symptoms

Drug Clinical Highlights:

- Orladeyo is the first FDA-approved, orally administered, non-steroidal option for prevention of HAE attacks
- Contraindications: none
- Warnings: doses should not exceed 150 mg per day due to an increased risk for QT prolongation at higher doses
- Adverse reactions (≥ 10%): abdominal pain, vomiting, diarrhea, back pain, gastroesophageal reflux disease
- Drug interactions:
  - P-gp or BCRP inhibitors: reduce Orladeyo dose
  - P-gp inducers: avoid use
  - CYP2D6, CYP3A4, or P-gp substrates: appropriately monitor or dose titrate narrow therapeutic index drugs
- Efficacy was demonstrated in Part 1 of a multicenter, randomized, double-blind, placebo-controlled, parallel-group study (NCT03485911)

NCT03485911 Study Design Summary	
Study Population	• 120 participants (adults and adolescents ≥ 12 years of age) with Type I or II HAE • 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 • Median baseline attack rate was 2.9 per month • 70% of patients had a baseline attack rate of ≥ 2 attacks per month
Interventions	• Randomized to berotralstat 110 mg once daily, berotralstat 150 mg once daily, or placebo for 24-week study period (1:1:1) • Other prophylactic HAE medications discontinued prior to study entry • Rescue medications for breakthrough acute attacks allowed

Primary Endpoint	• Reduction in HAE attack rate at 24 weeks
Efficacy Results	• 110 mg once daily (n=41): HAE attack rate 1.65, 30.0% reduction (p = 0.024) • 150 mg once daily (n=40): HAE attack rate 1.31, 44.2% reduction (p < 0.001) • Placebo (n=40): HAE attack rate 2.35

Price Per Unit (WAC):

$1,332.42 per capsule
$37,307.76 per 28 day pack

Therapeutic Alternatives:

- Therapies for HAE are categorized into treatment for acute attacks or treatment for prophylaxis of attacks.
- Current first-line therapies for long-term prophylaxis of HAE-C1INH include Cinryze®, Haegarda®, and Takhzyro®. Second-line therapies include anabolic androgens (i.e., Danazol) and antifibrinolytics (i.e., tranexamic acid or epsilon aminocaproic acid). Second-line therapies are reserved for when first-line therapies are unavailable or when the patient will only accept oral therapy.
- Long-term prophylaxis therapy in HAE-nl-C1INH has not been studied in randomized, placebo-controlled trials; however, hormonal therapy (stopping exogenous estrogen and using a progestin only therapy) and antifibrinolytics (tranexamic acid) are the most frequently used long-term prophylaxis agents for these patients. Due to its mechanism of action, Takhzyro is anticipated to be an effective therapy in this group as well; current guidelines state Takhzyro may be used for patients who fail hormonal therapy and antifibrinolytics.
- Orladeyo will compete with the injectable prophylactic therapies for prevention of HAE attacks. Although these agents have not been directly compared in clinical trials, a comparison of results from pivotal clinical trials is below. Orladeyo may be a viable option for patients with an aversion to injections and currently untreated with prophylactic therapy, especially in patients with mild or infrequent attacks.

	Cinryze	Haegarda	Takhzyro	Orladeyo
Mechanism of Action	C1 esterase inhibitor	C1 esterase inhibitor	Plasma kallikrein inhibitor	Plasma kallikrein inhibitor
Route of Administration	Intravenous	Subcutaneous	Subcutaneous	Oral
Dosing and Frequency	1,000 units (≥ 12 years) OR 500 units (6-11 years) twice weekly	60 units/kg twice weekly	300 mg once every 2 weeks	150 mg once daily
Age indication	≥ 6 years	≥ 6 years	≥ 12 years	≥ 12 years
Reduction in monthly attack rate vs. placebo	85%	95%	87%	44%
Cost per year (based on 80 kg patient)	$573,828	$518,566	$591,035	$485,000

Prior Authorization Approval Criteria:

Must meet the following criteria:

Initial Therapy:

- Documented diagnosis of hereditary angioedema (ICD-10: D84.1) **AND**
- Documentation of all of the following:
  - History of recurrent angioedema in the absence of concomitant urticaria or medication known to cause angioedema **AND**
  - Low (< 50% of normal) C1INH antigenic or functional level **AND**
  - Low C4 level (either at baseline or during an attack) **AND**
- Participant is aged ≥ 12 years **AND**
- Quantity limit of 1 capsule per day **AND**
- Failure to achieve desired therapeutic outcomes with trial of required number of preferred prophylactic therapies for HAE or documented ADE/ADR to preferred agents

Continuation of Therapy:

- Documented compliance on current therapy regimen

	Additional Provider Diagnostic/Monitoring Criteria, if desired: • Consider the need for appropriate on-hand therapy for treatment of an acute HAE attack
Implication to State Medicaid Program:	• LOE estimated in 2035 - 2036 • Orladeyo is currently being studied in a Phase 2 proof-of-concept trial as a treatment for acute HAE attacks. • Orladeyo is also being studied in a Phase 3 randomized, double-blind, placebo-controlled, dose-ranging trial as a single oral dose of a liquid formulation to be administered at home to treat HAE attacks.

References:

1. ORLADEYO™ (berotralstat) [package insert]. Durham, NC: BioCryst Pharmaceuticals, Inc.; December 2020.
2. CINRYZE® (C1 Esterase Inhibitor [Human]) [package insert]. Lexington, MA: Shire ViroPharma Incorporated; June 2018.
3. HAEGARDA® (C1 Esterase Inhibitor Subcutaneous [Human]) [package insert]. Kankakee, IL: CSL Behring LLC; September 2020.
4. TAKHZYRO® (lanadelumab-flyo) [package insert]. Lexington, MA: Dyax Corp; November 2018.
5. 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. 6 September 2020. https://doi.org/10.1016/j.jaip.2020.08.046.
6. Busse PJ, Christiansen SC. Hereditary Angioedema. N Engl J Med. 2020;382:1136-48. DOI: 10.1056/NEJMra1808012.
7. IPD Analytics. New Drug Review: Orladeyo (berotralstat). December 2020.
8. National Organization for Rare Disorders (NORD). Hereditary Angioedema. https://rarediseases.org/rare-diseases/hereditary-angioedema/. Accessed December 10, 2020.
9. National Center for Advancing Translational Sciences: Genetic and Rare Diseases Information Center. Hereditary angioedema. https://rarediseases.info.nih.gov/diseases/5979/hereditary-angioedema. Accessed December 10, 2020.