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Drug Class Update with New Drug Evaluation: Hereditary Angioedema

Date of Review: June 2021

Date of Last Review: March 2019
Dates of Literature Search: 01/01/2019 - 01/07/2021
Generic Name: berotralstat
Brand Name (Manufacturer): Orladeyo™ (BioCryst Pharmaceuticals, Inc)
Dossier Received: yes

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The purpose of this class update is to evaluate place in therapy for a new oral therapy for prophylaxis of hereditary angioedema (HAE) attacks.

Research Questions:
1. What is the comparative evidence for efficacy and harms of prophylactic therapy for HAE?
2. What is the efficacy and safety of berotralstat for prophylactic treatment of HAE attacks?
3. Are there subpopulations of patients with HAE for which treatment may be more effective or associated with more harms?

Conclusions:
- There is no new direct comparative evidence evaluating drugs for prophylaxis or acute treatment of HAE. Since the last review of this class, subcutaneous C1 esterase inhibitor concentrate from human plasma (Haegarda®) received an expanded indication for routine prophylaxis of hereditary angioedema attacks in patients 6-12 years of age.[1]
- Efficacy and safety of berotralstat was primarily based on a single, small, phase 3 trial evaluating efficacy over 24 weeks (n=121).[2]
- There is insufficient evidence evaluating efficacy of berotralstat to current prophylactic therapy for HAE. In patients with an average baseline of 3 HAE attacks per month, ongoing prophylactic use of berotralstat 150 mg daily decreases, but does not eliminate, HAE attacks compared to placebo (1.35 vs. 2.35 attacks per month; RR 0.56; 95% CI 0.41 to 0.77; p<0.001; low quality evidence).[3] All patients enrolled in the trial were required to have access to acute treatment for HAE attacks.
- There was no difference in quality of life for patients treated with berotralstat compared to placebo (insufficient evidence).[3] Berotralstat has not been studied for the treatment of acute attacks or for short-term prophylactic therapy prior to surgery. There is no evidence that prophylactic use of berotralstat treatments affects mortality, hospitalization rate, or has long-term impacts on work, school, depression or anxiety.
- The most common adverse events (AE) associated with berotralstat were gastrointestinal and primarily resolved with time.[2] Safety labeling includes warnings for QT prolongation and elevated liver enzymes.[2] There is insufficient data to evaluate long-term safety outcomes.

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Recommendations:

- Update prior authorization criteria to include berotralstat.
- No changes to the PDL were made based on clinical evidence or after evaluation of costs in executive session.

Summary of Prior Reviews and Current Policy

- Therapy for HAE can be divided into 2 types: acute and prophylactic treatment. There is no direct comparative evidence evaluating drugs for either prophylactic or acute treatment of HAE.
- With acute use for treatment of a HAE attack, time to symptom relief or resolution was improved by approximately 1-2 hours compared to placebo with human or recombinant C1 inhibitors or kallikrein inhibitors (low quality evidence).[4-8] The clinical benefit of a 1-2 hour improvement in symptoms in unclear, and there is insufficient evidence to evaluate efficacy of drugs in patients with laryngeal attacks.
- In patients with a frequent history of angioedema attacks (baseline rate of 3-4 per month), prophylactic use of C1 esterase inhibitors was associated with a mean reduction of 2.1 to 3.5 attacks per month over 12 to 16 weeks compared to placebo (low to moderate quality evidence).[9] With prophylactic use of lanadelumab compared to placebo in patients with a baseline rate of 3-4 attacks per month, the average angioedema attack rate was reduced by 1.5 to 1.7 attacks per month compared to placebo (moderate quality evidence).[9]
- There is insufficient evidence that prophylactic use of HAE treatments affects mortality, hospitalization rate, quality of life, or long-term impacts on work, school, depression or anxiety.

Background:

Hereditary angioedema (HAE) is caused by a deficiency or lack of function of C1 inhibitor protein.[10,11] C1 inhibitor is an important regulator of the complement system and the kallikrein-kinin pathway which is involved in formation of bradykinin.[11] A lack of functional C1 inhibitor protein can result in an overproduction of bradykinin which is the primary cause of swelling in patients with hereditary angioedema. The deficiency is most commonly hereditary, though it may also be acquired via increased catabolism of C1 inhibitor protein, often as a result of malignancy or autoantibodies, thereby decreasing inhibitor function. [11] Diagnosis is based on laboratory analysis of complement C4 and C2 levels and C1 inhibitor antigenic levels. [10,11] There are 3 types of HAE. Type 1 and type 2 are clinically indistinguishable from each other and account for the majority of cases of C1 inhibitor deficiency. Approximately 75% of patients diagnosed with HAE have a family history of angioedema. [11]

Symptoms of the disease include angioedema without urticaria which typically begin to present in early childhood or adolescence. Attacks of angioedema worsen gradually and resolve slowly over 24-72 hours. [11] Attacks may also be preceded by a prodromal phase with symptoms such as fatigue, non-urticarial rash, or other flu-like symptoms. Attacks most commonly involve the extremities and abdomen, but can be life-threatening if they involve the oropharynx or larynx. [11] Severity and frequency of attacks is highly variable between patients.[11] Frequency of attacks may be affected by hormone levels and often occur with onset of puberty, menopause, use of contraceptives, pregnancy, or other changes in estrogen levels. Hereditary angioedema is equally prevalent for males and females, though females may present with more frequent or severe symptoms due to changes in hormone levels. Precipitating factors for attacks are often unclear, though both stress and physical trauma have been correlated with onset of acute attacks. [10,11]

Current standard of care for treatment of acute attacks of angioedema include C1 inhibitors, ecallantide, or icatibant. Drugs that are FDA approved for acute and prophylactic therapy are shown in **Table 1**. While no high quality guidelines met inclusion criteria for this review, guidelines from the World Allergy Organization recommend on-demand therapy be considered for treatment of acute attacks of angioedema, and that any attack affecting the upper airway be treated (based

on expert consensus opinion).[10] Guidelines are limited by significant conflicts of interest and lack of details on guideline development methodology, with many recommendations based on expert consensus opinion. In general, early administration of medications is associated with better treatment response. [10] Recommended first-line prophylactic therapy includes a C1 inhibitor, though guidelines were published prior to FDA approval of lanadelumab-flyo or berotralstat.[10] No recommendations are made for a specific type of C1 inhibitor therapy. Administration of other anaphylactic therapy, such as epinephrine, antihistamines, and corticosteroids are only recommended if the cause of swelling and diagnosis of hereditary angioedema is unclear as these therapies do not improve symptoms of HAE attacks. [10]

Table 1. FDA-approved Indications and Dosing

Generic Name; Designation (Brand Name)	Indication(s)	Strength/Route	Dose and Frequency
Acute Treatment			
C1 esterase inhibitor; C1-INH-B (Berinert®)	Treatment of acute abdominal, facial, or laryngeal HAE attacks in adults and pediatric patients	500 units IV kit	20 units/kg as a single dose
C1 esterase inhibitor, recombinant ; C1-INH-R (Ruconest®)	Treatment of acute HAE attacks in adult and adolescent patients. Efficacy has not been established in laryngeal attacks	2100 units IV reconstituted solution	50 units/kg as a single dose; maximum dose: 4,200 units
Ecallantide (Kalbitor®)	Treatment of acute HAE attacks in patients 12 years and older	10 mg/mL SC solution	30 mg as a one-time dose (3 injections); may repeat once within 24 hours if attack continues
Icatibant (Firazyr®)	Treatment of acute HAE attacks in patients 18 years and older	10 mg/mL SC solution	30 mg once; may repeat every 6 hours if response is inadequate; maximum dose per day: 90 mg
Prophylactic Treatment			
Berotralstat (Orladeyo™)	HAE prophylaxis in patients ≥12 years of age	110 or 150 mg orally	150 mg daily; 110 mg daily recommended for patients with moderate to severe hepatic impairment or significant drug interactions
C1 esterase inhibitor ; C1-INH-C (Cinryze®)	HAE prophylaxis in adults, adolescents, and pediatric patients ≥6 years of age	500 units IV reconstituted solution	1,000 units every 3 to 4 days (twice weekly); doses up to 2,500 units (≤100 units/kg) every 3 or 4 days may be considered based on individual patient response.
C1 esterase inhibitor; C1-INH-H (Haegarda®)	HAE prophylaxis in adults and adolescents	2000 and 3000 units SC reconstituted solution	60 units/kg every 3 to 4 days (twice weekly)
Lanadelumab-flyo (Takhzyro™)	HAE prophylaxis in patients ≥12 years of age	300 mg/2mL SC solution	300 mg every 2 weeks; may consider dosing every 4 weeks for patients who are well-controlled for > 6 months

Abbreviations: HAE = hereditary angioedema, IV = intravenous; SC = subcutaneous

While plasma-derived products are screened extensively, there is still a risk for transmission of infectious disease (i.e., viruses) with plasma-derived C1 inhibitors (C1-INH-B, C1-INH-C, C1-INH-H).[12-14] Other major safety concerns include hypersensitivity reactions and thrombotic events which have been reported with both plasma-derived and recombinant C1 inhibitors.[12-15] Anaphylaxis is also a concern with ecallantide (reported in 3-4% of patients in clinical trials) and with C1

esterase inhibitors (incidence unknown).[8,10,16] Hypersensitivity reactions were also documented in 1% of patients treated with lanadelumab-flyo compared to placebo.[17] It is recommended that epinephrine be immediately available with administration of all human-derived C1 esterase inhibitors due to the risk of anaphylaxis. After self-administration of treatment for laryngeal HAE attacks, patients should be instructed to seek immediate medical care due to the ongoing potential for airway obstruction during acute laryngeal attacks.[10,16-18]

Clinically relevant outcomes include improvements in mortality, hospitalization rate, attacks requiring intubation or treatment, symptom severity, and impacts on work, school, or quality of life. Common outcomes evaluated in clinical trials include time to symptom resolution during an acute attack and reduction in number of attacks over time with prophylactic treatment. There is no established or validated measure to evaluate symptom improvement in patients with HAE attacks, and clinical trials have used a variety of scales to evaluate symptom severity and quality of life.

In the fee-for-service (FFS) population, approximately 11 patients had a diagnosis indicating defects in the complement system (D84.1) over a recent one year period. This number may be an overestimate of patients as this diagnosis includes conditions with other types of complement deficiencies.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
No high quality systematic reviews were identified since the last review.

New Guidelines:
No new high quality guidelines were identified since the last review.

New Formulations or Indications:
In September 2020, subcutaneous C1 esterase inhibitor concentrate from human plasma (Haegarda®) received an expanded indication for routine prophylaxis of hereditary angioedema attacks in patients 6 years and older.[1] The product was previously approved in adults and adolescents and expanded approval in children was based on a phase 3, open-label, long-term safety study. Nine pediatric patients ages 8 to 16 were included. Upon analysis by age, results were similar to the overall population.[1]

New FDA Safety Alerts:
No new safety alerts identified.

Randomized Controlled Trials:
A total of 21 citations were manually reviewed from the initial literature search. After further review, 19 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trials are summarized in the evidence table for berotralstat below.

NEW DRUG EVALUATION:

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Berotralstat was FDA approved based on a single phase 3, double-blind, placebo-controlled clinical trial of 121 patients with type 1 or 2 HAE.[3] Included patients were primarily White (>95%), and had an average of 3 HAE attacks per month. Most patients (approximately 75%) had a history of other prophylactic treatment for HAE.[3] Patients with fewer than 2 attacks over 8 weeks were excluded.[3] The primary endpoint was improvement in investigator-confirmed HAE attacks per month over 24 weeks. Secondary endpoints included change in quality of life, measured by the AE-QOL questionnaire, and number of days with angioedema symptoms. A second, similarly designed, smaller phase 3 trial including 19 patients was conducted in Japan.[19]

Trial limitations included slight variability between groups in prior treatments, age, gender, and body mass index (BMI) likely due to small sample sizes.[3] Groups were blinded with use of matched placebo, though characteristics of the placebo were not described, and differential rates of dose-related gastrointestinal AE between groups increases risk for potential unblinding. The majority of study authors had conflicts of interest including pending patents, personal fees from the manufacturer, or positions on speaker or advisory boards.[3] Applicability was limited to patients with frequent attacks (at least 2 per month). While patients were required to have at least 2 attacks during the screening period which impacted function or required treatment, the primary outcome evaluated all HAE attacks, not only those requiring treatment.[3] Confirmation of swelling was required to diagnose an attack, but it was unclear whether criteria was standardized between investigators for identification of attacks from patient diaries.

At 24 weeks compared to placebo, the number of investigator confirmed attacks per month was improved with both 110 mg (1.65 vs. 2.35; RR 0.70; 95% CI 0.51 to 0.95; p=0.024) and 150 mg (1.35 vs. 2.35; RR 0.56; 95% CI 0.41 to 0.77; p<0.001).[3] Similar trends were observed in the study in Japan, though results failed to achieve statistical significance for the 110 mg dose.[19] Authors noted that the study conducted in Japan had a small number of patients enrolled and was underpowered which is reflected in wide confidence intervals for the primary endpoint.[19] In the primary trial, there was no statistical difference observed for the secondary endpoint evaluating quality of life.[3] Other secondary endpoints were considered to be non-significant based on the pre-specified hierarchical testing plan.[3]

There is insufficient evidence evaluating efficacy of berotralstat to current prophylactic therapy for HAE. Trials to evaluate long-term efficacy and safety are ongoing. In patients with 2 or more HAE attacks per month, ongoing prophylactic use of berotralstat decreases, but does not eliminate HAE attacks. There is insufficient evidence that berotralstat does not improve quality of life for patients with HAE compared to placebo. There is currently no evidence for use in treatment of acute attacks or for short-term prophylactic therapy prior to surgery.

Clinical Safety:
Safety data for berotralstat was primarily based on a single, small, phase 3 trial evaluating efficacy over 24 weeks (n=121).[2] Few serious adverse events occurred during the trial, and the number of patients discontinuing treatment due to an adverse event was small (4 patients treated with berotralstat compared to 1 treated with placebo).[3]

Common adverse events occurring with berotralstat included abdominal pain, vomiting, diarrhea, back pain and gastroesophageal reflux disease (**Table 1**).[2] Gastrointestinal adverse events were dose dependent. Most gastrointestinal adverse events did not require intervention and typically self-resolved with time. However, use of the lower 110 mg dose is recommended in patients unable to tolerate 150 mg daily.[2]

Table 1. Common adverse events associated with berotralstat[2]

	Berotralstat* N (%)	**Placebo N (%)**	**Percent Difference**
Diarrhea	10 (12%)	0 (0%)	12%
Vomiting	10 (12%)	1 (3%)	9%
Gastroesophageal reflux disease	6 (7%)	0 (0%)	7%
Abdominal pain	13 (16%)	4 (10%)	6%
Back pain	5 (6%)	1 (3%)	3%

* Incidence for 110 and 150 mg daily combined

Labeling for berotralstat includes risks for QT prolongation with doses over 150 mg daily.[2] Liver-related adverse events also occurred in 3 patients treated with berotralstat including asymptomatic elevated transaminases (ALT >8x and AST >3x the upper limit of normal).[2] Berotralstat is metabolized by CYP enzymes and dose adjustment is recommended for patients with moderate or severe liver impairment to mitigate risk for QT prolongation.[2] Dose adjustment is also recommended in patients prescribed p-glycoprotein or BCRP inhibitors (e.g., cyclosporine).[2] Concomitant use of berotralstat with p-gp inducers is not recommended due to potential for decreased efficacy.[2]

There are insufficient data to assess the long-term safety of berotralstat. While berotralstat is FDA-approved in adolescents at least 12 years of age, only 16 adolescent patients were enrolled in clinical trials.[2] Similarly, a small number of geriatric patients 65 years or older were enrolled in clinical trials (n=14).[2] Subgroup analyses based on age identified no additional safety concerns in these populations, but data are significantly limited by the small number of patients included in clinical trials which limits ability to detect rare, but serious, adverse events.

Look-alike / Sound-alike Error Risk Potential: Berotralstat may be confused with belinostat or vorinostat, drugs used for the treatment of T-cell lymphoma.

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Hospitalizations
2) HAE attacks requiring treatment or intubation
3) HAE symptom severity (e.g., swelling, etc)
4) Functional improvement (e.g., missed work/school, etc)
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Investigator-confirmed HAE attacks per month

Table 2. Pharmacology and Pharmacokinetic Properties.[2]

Parameter	
Mechanism of Action	Berotralstat is a kallikrein inhibitor. Inhibition of kallikrein results in reduced blood levels of bradykinin thereby decreasing vascular permeability and edema in patients with HAE. Patients with C1-inhibitor deficiency (a endogenous kallikrein inhibitor) have increased activity of kallikrein which results in HAE symptoms.
Oral Bioavailability	Not reported
Distribution and Protein Binding	Protein binding: 99%
Elimination	9% excreted in urine and 79% excreted in feces
Half-Life	Median 93 hours (range: 39 to 152 hours)
Metabolism	Substrate of BCRP and p-glycoprotein. Metabolized by CYP2D6 and CYP3A4 enzymes.

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Zuraw, et al.[3] Phase 3, DB, PC, PG, MC, RCT	1. berotralstat 110 mg once daily 2. berotralstat 150 mg once daily 3. Placebo Run-in period of up to 70 days was used to evaluate baseline attack rate Acute treatment of attacks followed the patient's usual medical management Duration: 24 weeks	Demographics: - Age (SD) 1. 40 (17.5) 2. 40 (14.0) 3. 45 (14.1) - Female: 58-73% - White: 93-95% - North America: 68-78% - Normal BMI: 20-46% - Mean HAE attacks (SD) 1. 2.97 (1.36) 2. 3.06 (1.56) 3. 2.91 (1.12) - HAE attacks ≥2/month 1. 68% 2. 75% 3. 68% - Prior HAE tx: 73-78% - Prior C1-INH tx: 39-53% - Prior androgen tx: 46-63% Key Inclusion Criteria: - Age ≥12 years in Canada/US or ≥ 18 years in Europe - HAE type 1 or 2 confirmed by one of the following: - C1-INH functional level <50% and C4 level < LLN - C1-INH functional level 50%-74% with single-repeat level <50% or a pathogenic SERPING1 mutation - C4 level > LLN with low C4 during a HAE attack, physician confirmed family history of C1-INH deficiency or pathogenic SERPING1 - ≥ 2 attacks in 8 weeks with functional impairment or requiring treatment	ITT: 1. 41 2. 40 3. 40 Attrition: 1. 4 (9.8%) 2. 3 (7.5%) 3. 5 (12.5%)	Primary Endpoint: Investigator-confirmed HAE attacks per month 1. 1.65 2. 1.35 3. 2.35 1 vs. 3: RR 0.70 (95% CI 0.51-0.95); p=0.024 2 vs. 3: RR 0.56 (95% CI 0.41-0.77); p<0.001 Secondary Endpoints: Mean change in AE-QoL from baseline to week 24 (range 0-100) 1. –12.46 (SE 2.53) 2. –14.59 (SE 2.59) 3. –9.69 (SE 2.64) 1 vs. 3: –2.77 (–10.08 to 4.53); p = 0.453 2 vs. 3: –4.90 (–12.23 to 2.43); p = 0.118 Proportion of days with angioedema symptoms 1. 0.134 (SE 0.019) 2. 0.119 (SE 0.019) 3. 0.197 (SE 0.020) 1 vs. 3: –0.062 (95% CI –0.117 to –0.008)* 2 vs. 3: –0.078 (95% CI –0.133 to –0.023)* Mean number of days with angioedema symptoms 1. 20.8 (SD 19.22) 2. 19.4 (SD 21.50) 3. 29.2 (SD 24.29) Difference NR* *NS based on pre-specified hierarchical testing plan	 NA NA NS NS NS NS NS	DC due to AE 1. 3 (7.3%) 2. 1 (2.5%) 3. 1 (2.5%) Treatment emergent SAE 1. 1 (2.4%) 2. 0 (0%) 3. 3 (7.5%) Treatment emergent AE 1. 34 (83%) 2. 34 (85%) 3. 30 (77%) Gastro-intestinal abdominal treatment emergent AE 1. 17 (42%) 2. 20 (50%) 3. 14 (36%)	N/A For all	**Risk of Bias (low/high/unclear)**: Fair Selection Bias: Low. Randomized using interactive web response system. Stratified by baseline attack rate (< or ≥ 2 per month). Patients, investigators, site and sponsor personnel blinded to allocation. Slight variability between groups in prior treatments, age, gender, and BMI likely due to small sample sizes. Performance Bias: Unclear. Patients, investigators, site and sponsor personnel blinded via matching placebo. Differential rates of dose-related gastrointestinal AE between groups increases risk for potential unblinding. Detection Bias: Unclear. Patients and investigators blinded, but method of blinding unspecified. Use of patient reported diaries to document HAE attack symptoms with investigator follow-up and confirmation within 2 days. Confirmed swelling was a requirement to diagnose an attack, but it was unclear whether criteria was standardized between investigators for identification of attacks from patient diaries. Attrition Bias: Low. Attrition comparable between groups. ITT analysis used for efficacy outcomes. Reporting Bias: Low. Primary and secondary outcomes reported as pre-specified. Multiple post-hoc analyses. Other Bias: High. Study funded by manufacturer. Majority of authors with conflicts of interest including pending patents, personal fees from the manufacturer, or positions on speaker or advisory boards. Involvement of authors in data analysis was not reported. **Applicability**: Patient: Majority of patients were White. Patients included had frequent attacks (at least 2 attacks over 8 weeks); most patients had prior prophylactic therapy (75%) and a history of laryngeal attacks (74%). During the screening period, attacks had to cause functional impairment or require treatment. One-hundred sixty patients were screened and 121 had ≥2 attacks and enrolled. Intervention: Mean rate of compliance was 97-99% for all groups. Standard of care given for acute attacks. FDA-approved doses of 110 mg and 150 mg were evaluated. This trial demonstrated a small dose response. Doses were based on a phase 2 trial evaluating 62.5mg to 350mg. No statistical benefit was observed for 62.5mg dose compared to placebo, and doses of 250mg and 350 mg were not demonstrably different from the 125mg dose.[20]

		- Weight ≥ 40 kg Key Exclusion Criteria: - Use of androgen or tranexamic acid prophylaxis within 28 days or C1-INH prophylaxis within 14 days						Comparator: Placebo appropriate to determine efficacy. No comparison to available prophylactic therapies which would be useful to establish place in therapy. Outcomes: Primary endpoint counted all HAE attacks regardless of severity, not only those requiring treatment or functional impairment. Setting: 40 sites in 11 countries from March 14, 2018 to April 10, 2019. Numbers of patients in the US were not reported.
2. Ohsawa, et al.[19] Phase 3, DB, PC, PG, RCT	1. berotralstat 110 mg once daily 2. berotralstat 150 mg once daily 3. Placebo Run-in period of 56 days was used to determine eligibility and baseline HAE attacks Duration; 24 weeks Acute attacks were treated as needed by the investigator or treating physician	Demographics: - Mean age 42 years (SD 13) - Female: 84% - Asian: 94% - Mean BMI: 25 (SD 5) kg/m^2 - Attacks/month: 2.3 (SD 1.2) - HAE attacks ≥2/month: 48% - Prior prophylactic tx: 79% - C1-INH: 16% - Androgen: 16% - Tranexamic acid: 58% - Mean age at diagnosis: 31 (SD 14) - Missed work/education for HAE in prior year: 74% Key Inclusion Criteria: - Age ≥12 years - HAE type 1 or 2 (see Zuraw et al for specific diagnostic criteria) - ≥2 independent expert-confirmed HAE attacks during the run-in period Key Exclusion Criteria: - See Zuraw, et al	ITT: 1. 6 2. 7 3. 6 PP: 1. 6 2. 7 3. 5 Attrition: 1. 0 2. 0 3. 1 (17%)	Primary Endpoint: Expert-confirmed HAE attacks over 24 weeks 1. 1.64 2. 1.11 3. 2.18 1 vs. 3: RR 24.6% (95% CI −14.0 to 50.1); p=0.181 2 vs. 3: RR 49.1% (95% CI 20.4 to 67.5); p=0.003 Secondary Endpoints: Proportion of days with angioedema symptoms 1. 0.26 (SE 0.05) 2. 0.12 (SE 0.05) 3. 0.24 (SE 0.05) 1 vs. 3: 0.02 (95% CI −0.14 to 0.18); p=0.814* (mean of ~3 symptom free days) 2 vs. 3: −0.12 (95% CI −0.28 to 0.04); p=0.120 (~mean of ~20 symptom free days) Mean change in AE-QoL from baseline to week 24 (range 0-100) 1. −9.47 (SE 6.93) 2. −15.82 (SE 6.42) 3. 3.18 (SE 6.83) 1 vs. 3: −12.7 (95% CI −33.3 to 8.0); p=0.213 2 vs. 3: −19.0 (95% CI −39.0 to −1.0); NS* *NS based on pre-specified hierarchical testing plan	NS NA NS NS NS NS	Drug-related Treatment emergent AE 1. 2 (33%) 2. 2 (29%) 3. 2 (0%) DC due to AE 1. 0 (0%) 2. 0 (0%) 3. 1 (17%) Treatment emergent SAE 1. 1 (17%) 2. 0 (0%) 3. 0 (0%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized via interactive response system. Stratified by baseline attack rate (< or ≥ 2 attacks/month). Study drug assignment was blinded to the investigator, study staff, patients, and clinical research organization staff. Slight differences in baseline characteristics likely due to small sample sizes. Performance Bias: Unclear. Method of blinding not reported. Detection Bias: Unclear. Method of blinding unspecified. Use of patient reported diaries to document HAE attack symptoms with investigator follow-up and confirmation within 2 days. An independent expert reviewed information from all reported HAE attacks to confirm diagnosis. Attrition Bias: Low. Attrition comparable between groups. ITT analysis used for efficacy outcomes. Reporting Bias: Low. Outcomes reported as prespecified. Multiple post-hoc analyses reported. Other Bias: Unclear. Study funded by manufacturer. Majority of authors with conflicts of interest. Study was underpowered based on statistical power estimates and number of enrolled patients, which may result in limited ability to determine statistical differences between groups. **Applicability**: Patient: Of the 25 patients screened, 19 patients had ≥2 attacks and were randomized. Intervention: See Zuraw, et al. Comparator: See Zuraw, et al. Outcomes: Primary endpoint counted all HAE attacks regardless of severity, not only those requiring treatment or functional impairment. Attacks did not have to be unique events. Setting: 10 sites in Japan from December 2018 to November 2019.

Abbreviations [alphabetical order]: AE = adverse event; AE-QoL = Angioedema Quality of Life questionnaire; ARR = absolute risk reduction; BMI = body mass index; C1-INH = complement 1 inhibitor; C4 = complement 4; CI = confidence interval; DB = double blind; DC = discontinuation; HAE = hereditary angioedema; ITT = intention to treat; LLN = lower limit of normal; MC = multicenter; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = non-significant; NR = not reported; PC = placebo controlled; PG = parallel group; PP = per protocol; RCT = randomized controlled trial; SAE = severe adverse event; SD = standard deviation; SE = standard error

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
C1 esterase inhibitor	BERINERT	IV	KIT	Y
C1 esterase inhibitor	BERINERT	IV	VIAL	Y
C1 esterase inhibitor	HAEGARDA	SQ	VIAL	Y
berotralstat hydrochloride	ORLADEYO	PO	CAPSULE	
C1 esterase inhibitor	CINRYZE	IV	VIAL	N
C1 esterase inhibitor, recomb	RUCONEST	IV	VIAL	N
ecallantide	KALBITOR	SQ	VIAL	N
icatibant acetate	FIRAZYR	SQ	SYRINGE	N
icatibant acetate	ICATIBANT	SQ	SYRINGE	N
lanadelumab-flyo	TAKHZYRO	SQ	VIAL	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to January 07, 2021

1	exp Angioedemas, Hereditary/	1160
2	exp complement c1 inactivator proteins/ or exp complement c1 inhibitor protein/	2757
3	exp Bradykinin Receptor Antagonists/	1330
4	ecallantide.mp.	180
5	icatibant.mp.	1395
6	lanadelumab.mp.	44
7	berotralstat.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	3
8	BCX7353.mp.	5
9	2 or 3 or 4 or 5 or 6 or 7 or 8	4776
10	1 and 9	806
11	limit 10 to (english language and humans)	749
12	limit 11 to yr="2018 -Current"	157
13	limit 12 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or equivalence trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	21

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ORLADEYO™ safely and effectively. See full prescribing information for ORLADEYO™.

ORLADEYO™ (berotralstat) capsules, for oral use
Initial U.S. Approval: 2020

----------INDICATIONS AND USAGE----------
ORLADEYO is a plasma kallikrein inhibitor indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adults and pediatric patients 12 years and older. (1)

Limitations of Use:
ORLADEYO should not be used for treatment of acute HAE attacks. (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended Dosage: One capsule (150 mg) taken orally once daily with food. (2.1)

See Full Prescribing Information for:
- Dosage adjustment in patients with moderate or severe hepatic impairment. (2.2)
- Dosage adjustment in patients with chronic administration of P-gp or BCRP inhibitors. (2.3)
- Dosage adjustment in patients with persistent gastrointestinal reactions. (2.4)

----------DOSAGE FORMS AND STRENGTH----------
Capsules: 150 mg, 110 mg (3)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
An increase in QT prolongation can occur at dosages higher than the recommended 150 mg once daily dosage. Additional doses or doses of ORLADEYO higher than 150 mg once daily are not recommended. (5.1)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥10%) are abdominal pain, vomiting, diarrhea, back pain, and gastroesophageal reflux disease. (6.1)

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.

----------DRUG INTERACTIONS----------
P-gp or BCRP inhibitors – Reduce ORLADEYO dosage when co-administered. (7.1, 12.3)

P-gp inducers – Avoid use with ORLADEYO. (7.1)

CYP2D6, CYP3A4 or P-gp Substrates: Appropriately monitor or dose titrate narrow therapeutic index drugs that are predominantly metabolized by CYP2D6, CYP3A4 or are P-gp substrates when co-administered with ORLADEYO. (7.2, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2020

Appendix 4: Key Inclusion Criteria

Population	Patients with hereditary angioedema
Intervention	Drugs in Appendix 1
Comparator	Drugs in Appendix 1
Outcomes	Morbidity, mortality, symptom severity, attack rate, quality of life, functional status
Setting	Outpatient

Appendix 5: Prior Authorization Criteria

Hereditary Angioedema

Goal(s):

- To promote safe and effective use of hereditary angioedema treatments.

Length of Authorization:

- Up to 12 months

Requires PA:

- All pharmacotherapy for hereditary angioedema (pharmacy and physician administered claims).

  NOTE: This policy does not apply to hereditary angioedema treatments administered during emergency department visits or hospitalization.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. FDA Approved indications and dosing for hereditary angioedema treatments

Drug Name	Place in Therapy	FDA Indication(s)	Dose and Frequency
C1 esterase inhibitor (Berinert®)	Acute	Abdominal, facial, or laryngeal attacks	20 units/kg intravenously as a single dose
C1 esterase inhibitor, recombinant (Ruconest®)	Acute	Attacks in adults and adolescents. Efficacy has not been established in laryngeal attacks.	50 units/kg intravenously as a single dose; maximum dose: 4,200 units; may repeat once within 24 hours if attack continues

Ecallantide (Kalbitor®)	Acute	Attacks in patients ≥12 years of age	30 mg as a one-time dose (3 subcutaneous injections); may repeat once within 24 hours if attack continues
Icatibant (Firazyr®)	Acute	Attacks in adults ≥18 years of age	30 mg injection once; may repeat every 6 hours if response is inadequate; maximum dose per day: 90 mg
C1 esterase inhibitor (Cinryze®)	Prophylaxis	HAE prophylaxis in patients ≥6 years of age	1,000 units intravenously every 3 to 4 days (twice weekly); doses up to 2,500 units (≤100 units/kg) every 3 or 4 days may be considered based on individual patient response.
C1 esterase inhibitor (Haegarda®)	Prophylaxis	HAE prophylaxis in patients ≥6 years of age	60 units/kg subcutaneous every 3 to 4 days (twice weekly)
Berotralstat (Orladayo™)	Prophylaxis	HAE prophylaxis in patients ≥12 years of age	110 mg or 150 mg orally daily
Lanadelumab-flyo (Takhzyro™)	Prophylaxis	HAE prophylaxis in patients ≥12 years of age	300 mg subcutaneous injection every 2 weeks; may consider dosing every 4 weeks for patients who are well-controlled for > 6 months

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this a request for continuation of prophylactic therapy OR for treatment of a second acute attack previously approved through fee-for-service?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #3
3. Is the request for an FDA approved indication and place in therapy according to **Table 1** and is there confirmed laboratory diagnosis of hereditary angioedema (e.g., low C4 levels and either low C1 inhibitor antigenic levels or low C1 inhibitor functional levels)?	**Yes**: Go to #4 Document labs	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the diagnosis funded by OHP?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
5. Has the provider documented discussion with the patient of risks (including thrombotic events and/or anaphylaxis) versus benefits of therapy?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness. Notify provider of potential serious adverse effects of therapy. See notes below.
6. Is the request for a C1 esterase inhibitor or ecallantide?	**Yes:** Go to #7	**No:** Go to #8
7. Is the patient prescribed concurrent epinephrine or do they have epinephrine on hand?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.
8. Is the medication intended to be administered by a non-healthcare professional (e.g., self-administered)?	**Yes:** Go to #9	**No:** Go to #10
9. Has the member received training on identification of an acute attack?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.
10. Is the request for treatment of an acute hereditary angioedema attack?	**Yes:** Go to #13 Document attack severity if available	**No:** Go to #11
11. Is the request for prophylactic use in a patient with a history of hereditary angioedema attacks?	**Yes:** Go to #12 Document baseline number of attacks in the last 6 months	**No:** Pass to RPh. Deny; medical appropriateness.
12. Have potential triggering factors for angioedema including medications such as estrogens, progestins, or angiotensin converting enzyme inhibitors been assessed and discontinued when appropriate?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
13. Will the prescriber consider a change to a preferred product? Message: Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Approve for the following recommended durations: Acute treatment: Approve based on standard FDA dosing for treatment of a single acute attack (see **Table 1**) Prophylactic treatment: Approve for up to 6 months or length of therapy, whichever is less.

Renewal Criteria		
1. Is the request for additional treatment for acute attacks?	**Yes:** Go to #2	**No:** Go to #5
2. Is there documented utilization and benefit of the initial approved dose?	**Yes:** Approve based on standard FDA dosing for treatment of a single acute attack (see **Table 1**). Document attack severity if available	**No:** Go to #3
3. Does the patient currently already have at least one on-demand dose for an acute attack?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #4

Renewal Criteria		
4. Is there documentation from the prescriber that an on-demand dose is necessary and risks of therapy continue to outweigh the benefits?	**Yes:** Approve based on standard FDA dosing for treatment of a single acute attack (see **Table 1**). Document attack severity if available	**No:** Pass to RPh. Deny; medical appropriateness.
5. Since initiation of therapy, has the number or severity of hereditary angioedema attacks decreased?	**Yes:** Go to #6 Document change in attack frequency or severity	**No:** Pass to RPh. Deny; medical appropriateness.
6. Has the patient been attack free for at least 6 months?	**Yes:** Go to #7	**No:** Approve for up to 12 months.
7. Is there documentation from the prescriber that they have evaluated continued necessity of long-term prophylactic treatment at the current dose?	**Yes:** Approve for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness.

<u>Notes on adverse effects of treatment:</u>

Berotralstat

- Doses above 150 mg daily have been associated with QT prolongation. Dose adjustment is recommended for patients with moderate to severe hepatic impairment or with concomitant p-glycoprotein or BCRP inhibitors. Avoid use with p-glycoprotein inducers.

C1 esterase inhibitors

- In clinical trials of patients with moderate to severe hereditary angioedema attacks, use of C1 esterase inhibitors improved the duration of symptoms by an average 1-2 hours compared to placebo. Prophylactic use has only been evaluated in patients with more than 2 attacks per month.
- Hypersensitivity reactions have been observed with C1 esterase inhibitors. Due to the risk of anaphylaxis, it is recommended that all patients prescribed human derived C1 esterase inhibitors have epinephrine immediately available.
- Serious arterial and venous thrombotic events have been reported with use of C1 esterase inhibitors, particularly in patients with pre-existing risk factors for thromboembolism. The exact incidence of thrombosis with C1 esterase inhibitors is unclear. In patients using prophylactic therapy with Cinryze®, over an average of 2.6 years, 3% of patients experienced thrombosis.

Ecallantide

- The average improvement in symptoms compared to placebo at 4 hours after treatment of an acute attack was 0.4 points on a 0-3 point scale.

- Ecallantide has a box warning for anaphylaxis. In clinical trials, 3-4% of patients treated with ecallantide experienced anaphylaxis. Risks of treatment should be weighed against the benefits.

Icatibant

- In clinical trials of icatibant for acute attacks, time to 50% overall symptom improvement was 17.8 hours better than placebo (19 vs. 2 hours). A second study demonstrated no difference from placebo in time to symptom improvement. There are no data available on quality of life, daily activities, physical or mental functioning with use of icatibant.

Lanadelumab-flyo

- Prophylactic use has only been evaluated in patients with more than 1 moderate-severe attack per month. Hypersensitivity reactions were observed in 1% of patients treated with C1 esterase inhibitors. Elevated liver enzymes were also observed more frequently with lanadelumab compared to placebo (2% vs. 0%), and the long-term safety is unknown.

P&T/DUR Review: 6/21 (SS); 3/19 (SS)
Implementation: 7/1/2021; 5/1/19