Berotralstat (ORLADEYO), C1 (Esterase) Inhibitor (BERINERT, CINRYZE, HAEGARDA, RUCONEST), Ecallantide (KALBITOR), Icatibant (FIRAZYR), Lanadelumab-flyo (TAKHZYRO)
Criteria for Use
April 2021

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.

The respective Product Information should be consulted for detailed prescribing information.

Exclusion Criteria

If the answer to the item below is met, then the patient should NOT receive berotralstat, a C1 (esterase) inhibitor, ecallantide, icatibant, or lanadelumab-flyo.

- ☐ Angioedema or abdominal pain not associated with C1 inhibitor deficiency

Inclusion Criteria

The answers to ALL of the following must be fulfilled in order to meet criteria.

- ☐ Restricted to VA / VA Community Care allergy/immunology or dermatology provider; or for use in Emergency Medicine/Urgent Care
- ☐ Diagnosis of Hereditary Angioedema due to C1 inhibitor deficiency (HAE-C1INH) as established by laboratory testing

Additional Inclusion Criteria

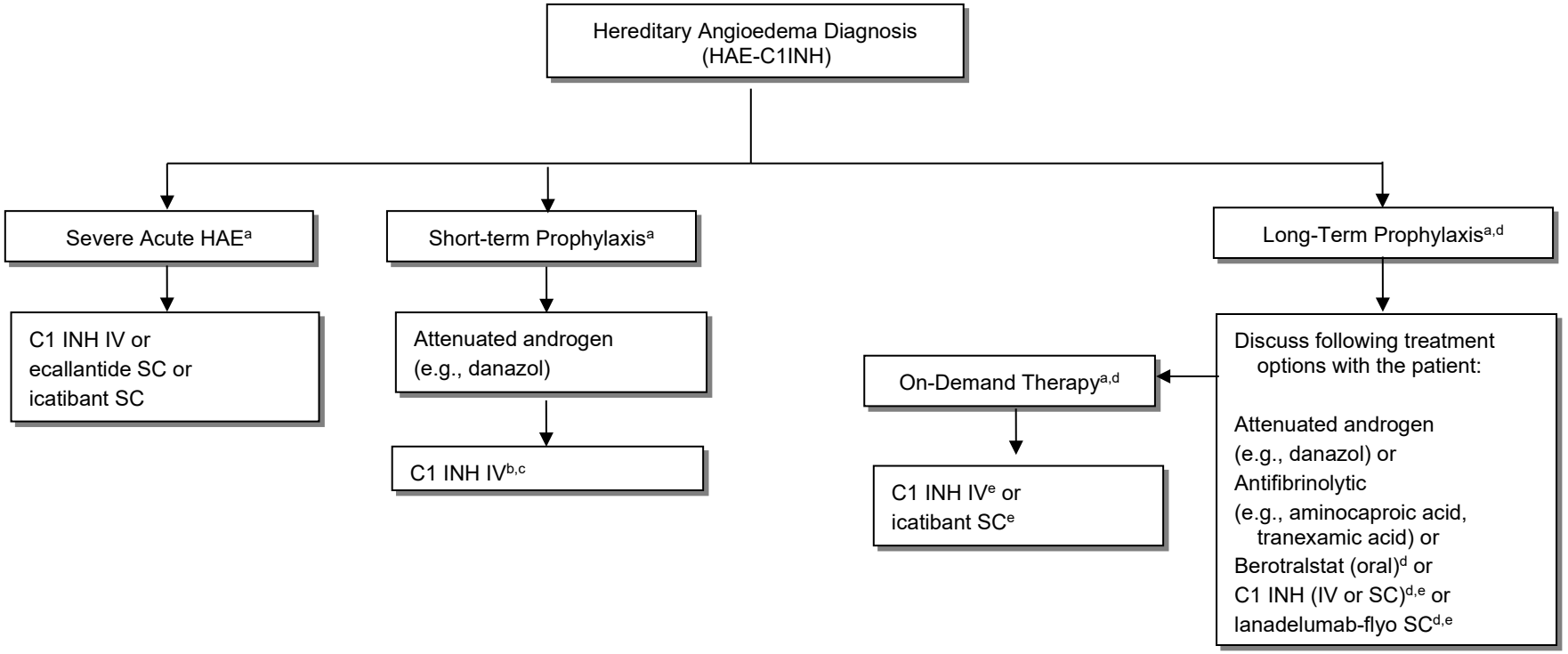
The answer to ONE of the following must be fulfilled in order to meet criteria.

- ☐ Diagnosis of severe acute HAE-C1INH [C1 inhibitor, ecallantide, or icatibant]. Symptoms may include: respiratory symptoms or laryngeal involvement, severe abdominal attack (severe pain with nausea and vomiting), significant orofacial swelling, etc. ^1
- ☐ Long-term prophylaxis [berotralstat, C1 Inhibitor, or lanadelumab-flyo] for HAE-C1INH attacks (^2) (^3) and after consideration of either an attenuated androgen or antifibrinolytic. ^4
- ☐ On-demand therapy [C1 inhibitor or icatibant] required for HAE-C1INH attacks despite long-term prophylaxis, or in a patient not receiving long-term prophylaxis. ^3
- ☐ Short-term prophylaxis for a major procedure or intubation [C1 inhibitor](^5) AND intolerance, contraindication to, or inefficacy with previous trial of attenuated androgens (e.g. danazol).

1. Treatment with C1 inhibitor, ecallantide or icatibant in patients presenting with moderate HAE attack symptoms should be determined on a case by case basis (e.g., patient may respond to supportive care, symptom management, increased doses of attenuated androgens or antifibrinolytics); plasma (solvent/detergent-treated or fresh frozen) has also been used for acute HAE

2. e.g., at least 2 per month used as inclusion criteria or baseline attack rate in clinical trials
3. On-demand therapy may be considered prior to implementing long-term prophylaxis, and in addition to long-term prophylaxis; need for long-term prophylaxis and/or on-demand therapy should be determined using shared decision-making
4. The option to use an attenuated androgen or antifibrinolytic prior to considering berotralstat, a C1 Inhibitor, or lanadelumab-flyo should be discussed with the patient using shared decision-making including the efficacy, routes of administration, and side effects of each therapy
5. Off-label use: C1 Inhibitor intravenous (IV) formulation preferred (data not available for subcutaneous [SC] C1 Inhibitor) for short-term prophylaxis; published case reports available on use of icatibant in short-term prophylaxis

Supplementary Information: Hereditary Angioedema Treatment Selection Algorithm



[a] Refer to Inclusion Criteria
[b] C1 INH IV formulation preferred (data not available for C1 INH SC for short-term prophylaxis); published case reports available on use of icatibant SC in short-term prophylaxis
[c] Fresh Frozen Plasma has also been used
[d] May be appropriate to consider On-Demand Therapy prior to implementing Long-Term Prophylaxis
[e] Extensive education must be provided with patient and/or caregiver demonstration of understanding, and ability and willingness to administer treatment

Abbreviations
C1 INH = C1 esterase inhibitor; HAE = Hereditary Angioedema; IV = Intravenous; SC = Subcutaneous

Supplemental Information: Product Comparison					
Medication	**FDA indication**	**Treatment Comparison**	**Results**	**Warnings/Precautions**	**Product Description**
Berotralstat (ORLADEYO)	Prophylaxis to prevent attacks of HAE	Berotralstat 110 mg, 150 mg once daily vs. placebo	Attack rate/month vs. placebo: Berotralstat 110 mg (1.65; P=0.24); 150 mg (1.31; P<0.001); Placebo (2.35)	QT prolongation at doses higher than 150 mg daily	Oral plasma kallikrein inhibitor
Lanadelumab-flyo (TAKHZYRO)	Prophylaxis to prevent attacks of HAE	Lanadelumab 300 mg every 2 wks, 300 mg every 4 wks, 150 mg every 4 wks vs. placebo	Mean reduction in HAE attacks vs. placebo: Lanadelumab 300 mg every 2 wks (-1.71; P<0.001)); 300 mg every 4 wks (-1.44; P<0.001)); 150 mg every 4 wks (-1.49; P<0.001)	Hypersensitivity	Non-plasma derived, recombinant, fully human, monoclonal antibody produced in Chinese Hamster Ovary cells
C1 Inhibitor (HAEGARDA)	Routine prophylaxis to prevent HAE attacks	C1 INH 40 IU/kg 2 x/wk vs. placebo C1 INH 60 IU/kg 2 x/wk vs. placebo	Mean HAE attacks/month: C1 INH 40 IU/kg 1.19 vs. placebo 3.61 (mean difference -2.42/month; P<0.001) C1 INH 60 IU/kg 0.52 vs. placebo 4.03 (mean difference -3.51/month; P<0.001)	Hypersensitivity Risk for transmission of infectious agents Thrombotic events	Derived from human plasma (pasteurized, nanofiltered)
C1 Inhibitor (CINRYZE)	Routine prophylaxis against HAE attacks	Acute: C1 INH 1000 units IV vs. placebo Prophylaxis: C1 INH 1000 units IV 2 x/wk vs. placebo	PEP (Acute): 2 hrs vs. > 4 hrs (P=0.02) Median time to complete resolution: 12.3 hrs vs. 25 hrs (P=0.004) Prophylaxis: 6.26 vs. 12.73 attacks (P<0.001)	Hypersensitivity Risk for transmission of infectious agents Thrombotic events	Derived from human plasma (pasteurized, nanofiltered)
C1 Inhibitor (BERINERT)	Acute abdominal, facial or laryngeal attacks of HAE	C1 INH 10 or 20 units/kg IV vs. placebo	PEP (Acute): 0.5 hrs (20 units/kg) vs. 1.5 hrs (P=0.0025) Median time to complete resolution: 4.92 hrs vs. 7.79 hrs (P=0.0237)	Hypersensitivity Risk for transmission of infectious agents Thrombotic events	Derived from human plasma (pasteurized, nanofiltered)
C1 Inhibitor (RUCONEST)	Acute attacks HAE	C1 INH 50 units/kg IV vs. placebo	PEP (Acute): 90 min (1.5 hrs) vs. 152 min (2.53 hrs); (P=0.031) Median time to minimal sx: 303 min (5.05 hrs) vs. 483 min (8.05 hrs) (P=0.078)	Hypersensitivity Thrombotic events (reported with pdC1INH in patients with risk factors)	Recombinant analogue of human C1INH purified from the milk of transgenic rabbits
Ecallantide (KALBITOR)	Acute attacks HAE	Ecallantide 30 mg SC vs. placebo	PEP (Study 1): Median 50 vs. 0 (P=0.004) Median time to onset overall sx improvement: 2.75 hrs vs. > 4 hrs (P=0.14) PEP (Study 2): Median -1 vs. 0 (P=0.01)	Boxed warning for anaphylaxis	Amino acid protein produced in *Pichia pastoris* yeast cells by recombinant DNA technology
Icatibant (FIRAZYR)	Acute attacks HAE	(Study 1 & 3) Icatibant 30 mg SC vs. placebo (Study 2) Icatibant 30 mg SC vs. tranexamic acid 3 gm daily X 2 days	PEP (Study 1): 2.5 hrs vs. 4.6 hrs (P=0.14) Median time to almost complete sx relief: 8.5 hrs vs. 19.4 hrs (P=0.08) PEP (Study 2): 2.0 hrs vs. 12.0 hrs (P<0.001) Median time to almost complete sx relief: 10.0 hrs vs. 51.0 hrs (P<0.001) PEP (Study 3): 2.0 hrs vs. 19.8 hrs (P<0.001) Median time to almost complete sx relief: 8.0 hrs vs. 36.0 hrs (P<0.001)	Seek immediate medical attention if acute laryngeal HAE attack	Synthetic decapeptide with 5 non-proteinogenic amino acids

8/2010; updated 12/2010, 6/2012, 6/2015, 11/2017, 9/2019, 4/2021

Continued	Product availability	Dose	Route of Administration	Storage	Shelf-life	VA Special Handling
Berotralstat (ORLADEYO)	Oral capsules (150 mg, 110 mg) provided as 28-day supply in carton of four child-resistant shellpaks, each containing a 7-capsule blister card	150 mg once daily (110 mg once daily in patients requiring dose adjustments)	Oral	Room temperature (68° to 77° F)	36 months	Available to VA pharmacies by submitting Orladeyo Prescription Form for VA Patients to Optime Care Specialty Pharmacy
Lanadelumab-flyo (TAKHZYRO)	Ready-to-use solution in single-dose vial (additional reconstitution or dilution not required)	300 mg every 2 weeks (every 4 weeks option)	SC injection Instructions available for self-administration	Refrigerate (36° to 46° F) Do not freeze Protect from light	Up to 24 months	None
C1 Inhibitor (HAEGARDA)	Powder for reconstitution for SC injection in a single-use vial kit; kit packaged with sterile water (4 mL for reconstitution of 2000 IU or 6 mL for reconstitution of 3000 IU) and one Mix2Vial filter transfer set	60 IU/kg twice weekly (every 3 or 4 days)	SC injection Instructions available for self-administration	Up to 86° F Do not freeze Protect from light	Up to 36 months	Available to VA pharmacies by placing direct orders for the product by contacting CSL Behring (phone, fax, email)
C1 Inhibitor (CINRYZE)	Powder (500 units) for reconstitution with 5 mL sterile water using double-ended transfer needle for concentration 100 units/mL; combining 2 vials in syringe, with use of appropriate needle/IV administration set for delivery of 1000 units dose at rate of 1 mL/min over 10 min	1000 units every 3 or 4 days	IV infusion (1mL/min) (10 min per dose) Instructions and training available for self-administration	36° to 77° F Protect from light	Up to 24 months	Available for purchase from Curascript SD; can be dispensed by local VA pharmacy or specialty pharmacy
C1 Inhibitor (BERINERT)	Kit containing 500 units powder in single-use vial for reconstitution with 10 mL sterile water and Mix2Vial transfer set; required number of vials are reconstituted to obtain dose of 20 units per kg combined in syringe, with use of IV administration set to deliver dose at rate of 4 mL/min	20 units per kg	IV infusion (4 mL/min) (duration of infusion depends on dose based on weight) Approved for on-demand self-administration; instructions and training available	36° to 86° F Protect from light	Up to 30 months	Available for purchase from McKesson Plasma & Biologics; dispensed from local VA pharmacy
C1 Inhibitor (RUCONEST)	Available as a lyophilized powder for reconstitution for injection in a single-use 25 ml vial; each vial contains 2100 IU of rhC1INH	< 84 kg: 50 units per kg ≥ 84 kg: 4200 units	Slow IV infusion over 5 min Instructions and training available for self-administration	36° to 77° F Protect from light	Up to 48 months	Available for purchase from ASD Healthcare and Cardinal Health Specialty; no specialty pharmacy requirements
Ecallantide (KALBITOR)	Package containing 3 single-use vials each with 10 mg/mL (1 mL), with 3 separate SC injections required to administer dose of 30 mg	30 mg	SC injection (3 injections per dose) Recommendations to only be administered by healthcare professional with medical support available to manage anaphylaxis and HAE	Refrigerate (36° to 46° F) Protect from light	Up to 36 months	Available for purchase from ASD Healthcare; no specialty pharmacy requirements
Icatibant (FIRAZYR)	One ready-to-use pre-filled syringe of 30 mg/3 mL required to deliver 30 mg administered SC	30 mg	SC injection (one 3 mL injection) Instructions and training available for self-administration	36° to 77° F Store in container until ready to use	Up to 24 months	Available for purchase from McKesson; no specialty pharmacy requirements

C1 INH=C1 inhibitor; HAE=hereditary angioedema; hrs=hours; IV=intravenous; min=minute; OL=open-label; PI=product information; pd=plasma-derived; RCT=randomized controlled trial; rh=recombinant human; SC=subcutaneous; sx=symptom; TEQ=Treatment Effect Questionnaire; tx=treatment; VAS=visual-analogue scale

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