BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

HEREDITARY ANGIOEDEMA MEDICATION THERAPY: BERINERT® (plasma derived C1 esterase inhibitor) CINRYZE™ (plasma derived C1 esterase inhibitor) FIRAZYR® (icatibant, bradykinin B2 inhibitor) HAEGARDA® (C1 esterase inhibitor) Icatibant Acetate (bradykinin B2 inhibitor) KALBITOR (ecallantide) ORLADEYO™ (berotralstat, kallikrein inhibitor) RUCONEST® (recombinant human C1 esterase inhibitor) SAJAZIR™ (icatibant, bradykinin B2 inhibitor) TAKHZYRO™ (lanadelumab-flyo, kallikrein monoclonal antibody)

This Pharmacy Coverage Guideline (PCG):

- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope

- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance

- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

ORIGINAL EFFECTIVE DATE: 04/01/2019 | ARCHIVE DATE: | LAST REVIEW DATE: 11/16/2023 | LAST CRITERIA REVISION DATE: 11/16/2023

PHARMACY COVERAGE GUIDELINE

HEREDITARY ANGIOEDEMA MEDICATION THERAPY

Criteria:

Section A. Acute Attacks of Hereditary Angioedema (HAE):
BERINERT® (plasma derived C1 esterase inhibitor)
FIRAZYR® (icatibant, bradykinin B2 receptor antagonist)
Icatibant (bradykinin B2 receptor antagonist)
KALBITOR® (ecallantide, plasma kallikrein inhibitor) – not for self-administration
RUCONEST® (recombinant human C1 esterase inhibitor)
SAJAZIR™ (icatibant, bradykinin B2 receptor antagonist)

- **Criteria for initial therapy:** Berinert (pdC1INH), icatibant (generic, Firazyr, Sajazir), Kalbitor (ecallantide), or Ruconest (rhC1INH) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Allergist or Immunologist

2. Individual's age is consistent with FDA product label for the requested product

3. Individual has a confirmed diagnosis of recurrent episodes of acute attacks of hereditary angioedema (HAE) that requires therapy

4. Diagnosis of hereditary angioedema (HAE) is supported by **ONE** of the following:
   a. HAE C1 inhibitor (HAE-C1-INH) deficiency or dysfunction (Type I or II HAE) as documented by **ALL** of the following:
      i. Two sets C1-inhibitor (C1INH) showing low level (done at least one month apart)
      ii. Two sets C1-inhibitor (C1INH) showing low activity/function (done at least one month apart)
      iii. Two sets C4 showing low level (done at least one month apart)

   b. HAE C1 inhibitor levels are normal (HAE-nl-C1-INH, formerly Type III) and **ONE** of the following:
      i. Documentation of a positive family history of recurrent angioedema **and** documented lack of efficacy of high-dose antihistamine therapy (i.e., cetirizine at 40 mg/d or the equivalent) for at least 1 month (**or** an interval expected to be associated with 3 or more attacks of angioedema, whichever is longer)
      ii. Presence of a mutation specific for HAE with normal C1-INH (see Definitions section)

5. Individual does not have **any** of the following:
   a. Angioedema episodes from use of angiotensin-converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), or history to suggest an allergic cause
   b. Angioedema episodes that respond to antihistamines, glucocorticoids, epinephrine, or Xolair (omalizumab)
   c. Urticaria (hives) or pruritus (itching) with episodes of HAE

6. **ONE** of the following:
   a. Individual has trigger induced **acute** attacks of angioedema from a known precipitant (e.g., medical, surgical, or dental procedures) but does not require long-term prophylactic therapy

b. Individual has frequent or severe **acute** attacks of angioedema despite use of long-term prophylactic therapy

7. **Additional criteria for Firazyr (icatibant) and Sajazir (icatibant) only:** Documented failure, contraindication per FDA label, intolerance, or is not a candidate for generic icatibant

8. **Additional criteria for Kalbitor (ecallantide) only:**
   a. Kalbitor (ecallantide) will be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and HAE
   b. Use is contraindicated in an individual with known clinical hypersensitivity to Kalbitor (ecallantide)

9. Individual will **NOT** be using combination therapy with another agent for the treatment of acute attacks of angioedema unless provider submits justification for combination therapy

Initial approval duration: 6 months, for a quantity that is enough for treatment of two attacks with 1 refill

- **Criteria for continuation of coverage (renewal request):** Berinert, Icatibant (generic, Firazyr, Sajazir), Kalbitor (ecallantide), or Ruconest is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered as continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Allergist or Immunologist

2. Individual's condition has responded while on therapy with response defined as **ONE** of the following:
   a. Achieved and maintains at least a 50% reduction in the number of acute attacks of HAE
   b. Achieved and maintains at least a 30% in the duration of acute attacks of HAE
   c. Achieved and maintains at least a 60% reduction in the number of days with acute symptoms

3. Additional criteria for continuation of **Firazyr (icatibant) and Sajazir (icatibant)**: Individual has failure, contraindication per FDA label, or intolerance, or is not a candidate for equivalent generic icatibant

4. **Additional criteria for Kalbitor (ecallantide) only:**
   a. Kalbitor (ecallantide) will be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and HAE
   b. Use is contraindicated in an individual with known clinical hypersensitivity to Kalbitor (ecallantide)

5. Individual has been adherent with the medication

6. Individual does not have **any** of the following:
   a. Angioedema episodes from use of angiotensin-converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), or history to suggest an allergic cause
   b. Angioedema episodes that respond to antihistamines, glucocorticoids, epinephrine, or Xolair (omalizumab)
   c. Urticaria (hives) or pruritus (itching) with episodes of HAE

7. There is no evidence the individual has developed any significant unacceptable adverse drug effects from use of the agent that may exclude continued use

8. Individual will **NOT** be using combination therapy with another agent for treatment of acute attacks of angioedema unless provider submits justification for combination therapy

Renewal duration: 6 months, for a quantity that is enough for treatment of two attacks with 1 refill

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Section B. Prophylaxis of Attacks of Hereditary Angioedema (HAE): CINRYZE™ (plasma derived C1 esterase inhibitor) HAEGARDA® (plasma derived C1 esterase inhibitor) ORLADEYO™ (berotralstat, kallikrein inhibitor) TAKHZYRO™ (lanadelumab-flyo, kallikrein monoclonal antibody)

- **Criteria for initial therapy:** Cinryze, Haegarda, Orladeyo, or Takhzyro is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Allergist or Immunologist

2. Individual's age is consistent with FDA product label for the requested product

3. Individual has frequent or severe attacks of hereditary angioedema (HAE) that requires routine long-term prophylaxis

4. Diagnosis of hereditary angioedema (HAE) is supported by **ONE** of the following:
   a. HAE C1 inhibitor (HAE-C1-INH) deficiency or dysfunction (Type I or II HAE) as documented by **ALL** of the following:
      i. Two sets C1-inhibitor (C1INH) showing low level (done at least one month apart)
      ii. Two sets C1-inhibitor (C1INH) showing low activity/function (done at least one month apart)
      iii. Two sets C4 showing low level (done at least one month apart)

   b. HAE C1 inhibitor levels are normal (HAE-nl-C1-INH, formerly Type III) and of **ONE** of the following:
      i. Documentation of a positive family history of recurrent angioedema and documented lack of efficacy of high-dose antihistamine therapy (i.e., cetirizine at 40 mg/d or the equivalent) for at least 1 month (**or** an interval expected to be associated with 3 or more attacks of angioedema, whichever is longer)
      ii. Presence of a mutation specific for HAE with normal C1-INH (see Definitions section)

5. Individual does not have **any** of the following:
    a. Angioedema episodes from use of angiotensin-converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), or history to suggest an allergic cause
    b. Angioedema episodes that respond to antihistamines, glucocorticoids, epinephrine, or Xolair (omalizumab)
    c. Urticaria (hives) or pruritus (itching) with episodes of HAE

6. **ONE** of the following:
    a. Individual with HAE-C1-INH has frequent or severe acute attacks of angioedema and requires long term prophylaxis
    b. Individual with HAE-nl-C1-INH has frequent or severe acute attacks of angioedema and requires long term prophylaxis and the individual has documented failure, intolerance, contraindication per FDA label, or is not a candidate for **ONE of the following**
        i. Oral tranexamic acid
        ii. Progesterone-only contraceptives (in premenopausal female)
        iii. Androgen (generally in adult male)

7. **Additional criteria for Orladeyo only:**
    a. Individual does not have end stage renal disease (creatinine clearance of less than 15mL/min or estimated glomerular filtration rate less than 15 mL/min/m^2 or requiring hemodialysis)
    b. Individual is not on P-gp inducing agents such as rifampin, St. John's Wort, etc

8. Individual will **NOT** be using combination therapy with another agent for prevention/prophylaxis of attacks of HAE unless provider submits justification for combination therapy

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Cinryze, Haegarda, Orladeyo, or Takhzyro is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered as continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Allergist or Immunologist

2. Individual's condition has responded while on therapy with response defined as **ONE** of the following:
    a. Achieved and maintains at least a 50% reduction in the number of HAE attacks
    b. Achieved and maintains at least a 30% in the duration of HAE attacks
    c. Achieved and maintains at least a 60% reduction in the number of days with symptoms

3. Individual has been adherent with the medication

4. Individual does not have **any** of the following:
    a. Angioedema episodes from use of angiotensin-converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), or history to suggest an allergic cause
    b. Angioedema episodes that respond to antihistamines, glucocorticoids, epinephrine, or Xolair (omalizumab)
    c. Urticaria (hives) or pruritus (itching) with episodes of HAE

5. **Additional criteria for Orladeyo only:**
    a. Individual does not have end stage renal disease (creatinine clearance of less than 15mL/min or estimated glomerular filtration rate less than 15 mL/min/m^2 or requiring hemodialysis)
    b. Individual is not on P-gp inducing agents such as rifampin, St. John's Wort, etc
    c. The requested dose is **NOT** greater than 150 mg daily

6. There is no evidence the individual has developed any significant unacceptable adverse drug effects from use of the agent that may exclude continued use

7. Individual will **NOT** be using combination therapy with another agent for prevention/prophylaxis of attacks of HAE unless provider submits justification for combination therapy

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Benefit Type:

Pharmacy Benefit:
BERINERT
CINRYZE
FIRAZYR
HAEGARDA
Icatibant Acetate
ORLADEYO
RUCONEST
SAJAZIR
TAKHZYRO

Medical Benefit:
KALBITOR

Coding:

HCPCS: J1290

PHARMACY COVERAGE GUIDELINE

HEREDITARY ANGIOEDEMA MEDICATION THERAPY

Description:

Hereditary angioedema (HAE) is an autosomal dominant disorder that results from C1 esterase inhibitor (C1INH) deficiency. C1INH regulates the activity of the complement component C1, the first step in the classic complement cascade.

HAE is a disease characterized by recurrent episodes of angioedema, **without** urticaria or pruritus, most often affecting the skin or mucosal tissues of the upper respiratory and gastrointestinal tracts. People with HAE can develop rapid painful swelling of the hands, feet, limbs, face, intestinal tract, or airway. Acute attacks of swelling can occur spontaneously, or can be triggered by stress, surgery, medical or dental procedures, or infection. The swelling is often self-limited and resolves in two to five days without treatment, however laryngeal involvement may cause fatal asphyxiation.

The swelling (i.e., angioedema) that occurs in HAE results from excessive production of bradykinin, a potent mediator of vasodilation. Bradykinin also has important vascular permeability-enhancing effects. During episodes of angioedema individuals with HAE have plasma bradykinin levels shown to be substantially higher than normal

HAE is caused by low levels or inadequate function of a plasma protein called C1-esterase inhibitor (C1INH) that is involved in regulating how some portions of the immune system and blood clotting pathways work. The absence or dysfunction of C1INH leads to an increase in bradykinin production. Bradykinin dilates blood vessels which is responsible for the symptoms of HAE.

The angioedema of HAE mediated by bradykinin does not respond to epinephrine, antihistamines, or glucocorticoids.

Therapeutic approaches for HAE include both "on-demand" treatments given at the onset of symptoms to abolish angioedema attacks as well as prophylactic treatment used to prevent or minimize attacks. All individuals require a readily available on-demand treatment to terminate unpredictable angioedema episodes. Short-term prophylaxis is use of medication given before a known trigger such as specific medical or dental procedures. In contrast, long-term prophylaxis is given to decrease the number and length of attacks. An integral part of treatment is trigger avoidance, if possible.

Therapies that are minimally effective or have no benefit at all in the treatment of acute angioedema in HAE include androgens, tranexamic acid, and treatments for allergic (histaminergic) angioedema such as epinephrine. Glucocorticoids and antihistamines are NOT effective for angioedema associated with disorders of C1INH and should not be given once the diagnosis of a C1INH disorder has been made.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Comparison of complement studies in angioedema disorders

Angioedema disorder	C4*	C1-INH level	C1-INH function/activity	C1q	Other tests
HAE with C1-INH deficiency type I (**HAE-C1-INH type I**)	Low	Low	Low (usually < 50% of normal	Normal	Genetic testing (not needed for Dx)

HAE with C1INH deficiency type II (**HAE-C1-INH type II**)	Low	Normal or elevated	Low (usually < 50% of normal	Normal	Genetic testing (not needed for Dx)
Hereditary Angioedema Type III (HAE-III):					
HAE with **coagulation factor XII** gene mutations (HAE-FXII)	Normal	Normal	Normal	Normal	Mutations in gene for factor XII
HAE with **angiopoietin-1** gene mutations (HAE-ANGPT1)	Normal	Normal	Normal	Normal	Mutations in gene for angiopoietin-1
HAE with **plasminogen** gene mutations (HAE-PLG)	Normal	Normal	Normal	Normal	Mutations in gene for plasminogen
HAE with **kininogen-1** gene mutations (HAE-KNG1)	Normal	Normal	Normal	Normal	Mutations in gene for kininogen-1
HAE with **myoferlin** (HAE-myoferlin)	Normal	Normal	Normal	Normal	Mutation in the MYOF gene
HAE with **heparan sulfate-glucosamine 3-O-sulfotransferase 6**	Normal	Normal	Normal	Normal	Mutation in the gene HS3ST6
HAE of **unknown** origin (HAE-U)	Normal	Normal	Normal	Normal	Unknown
Acquired angioedema with C1-INH deficiency (AAE-C1-INH)	Low	Normal or low	Low (usually < 50% of normal)	Normal or low¶	Anti-C1-INH antibodies (not needed for diagnosis)
Idiopathic acquired angioedema (histaminergic or non-histaminergic) (AAE-IH or AAE-InH)	Normal	Normal	Normal	Normal	
ACE inhibitor-associated angioedema (AAE-ACEI)	Normal	Normal	Normal	Normal	

* In HAE-C1-INH types I and II, C4 is always low during an attack (with one published exception) and are chronically low in the majority of patients.
¶ There are rare forms of acquired angioedema in which C1q levels are normal.

Medications used for treating individuals with HAE:

Drug	Age	Route	Self-Administer	Dose	How supplied
On-demand medications for acute attacks HAE					
Plasma derived C1 esterase inhibitor (pdC1INH): **Berinert**	5	IV	Yes	20 IU per kg ***A second dose can be given 4 hours after the initial dose***	500 IU single-use vial

PHARMACY COVERAGE GUIDELINE

HEREDITARY ANGIOEDEMA MEDICATION THERAPY

Recombinant C1 esterase inhibitor (rhC1INH): **Ruconest**	13	IV	Yes	< 84 kg: 50 IU per kg ≥ 84 kg: 4200 units (2 vials) Max 4200 IU per dose ***No more than two doses in 24 hours, however a second dose is rarely needed***	2100 IU single-use vial
Bradykinin B2 Receptor antagonist: **Firazyr (icatibant)** **Icatibant** **Sajazir (icatibant)**	18	SQ	Yes	30 mg injected to the abdominal area Additional doses can be given after 6 hours. ***Max of three doses in 24 hours***	Single-dose, single-use, prefilled syringe with 30 mg per syringe packaged as single carton with one syringe or pack of three cartons each with one syringe
Kallikrein inhibitor: **Kalbitor (ecallantide)**	12	SQ	No	30 mg injected (3 doses of 10 mg (1 mL) each) given at three separate sites. ***A second dose can be given within 24 hours after the initial dose***	Three 10 mg/mL single-use vials packaged in a carton
Prophylaxis of HAE					
Plasma derived C1 esterase inhibitor (pdC1INH): **Cinryze**	6	IV	Yes	12 years and older: 1,000 units every 3 or 4 days Up to 2,000 units (80 U/kg) every 3 or 4 days 6-11 years of age: 500 units every 3 or 4 days Up to 1,000 units every 3 or 4 days	500 IU single-use vial
Plasma derived C1 esterase inhibitor (pdC1INH): **Haegarda**	6	SQ	Yes	60 IU per kg twice weekly (every 3 or 4 days)	2000 or 3000 IU single-use vials
Oral kallikrein inhibitor: **Orladeyo (berotralstat)**	12	PO	Yes	150 mg orally once daily or 110 mg orally once daily in patients with moderate or severe hepatic impairment; persistent GI events; and certain drug-drug interactions ***Additional doses or doses higher than 150 mg once daily are not recommended due to QT prolongation***	110 mg, 150 mg capsule
Kallikrein inhibitor monoclonal antibody: **Takhzyro (lanadelumab-flyo)**	2	SQ	Yes	12 years and older: 300 mg every 2 or 4 weeks 6 to less than 12 years of age: 150 mg every 2 or 4 weeks 2 to less than 6 years of age: 150 mg every 4 weeks	300 mg single-use vial 300 mg single-use syringe 150 mg single-use syringe

PHARMACY COVERAGE GUIDELINE

HEREDITARY ANGIOEDEMA MEDICATION THERAPY

Androgens:					
Danazol	16	PO	Yes	Approved for adults: 200 mg/d PO (100 mg every 3 d to 600 mg/d) Off-label for pediatric individuals: 50 mg/d PO (50 mg/week to 200 mg/d)	50 mg, 10 mg, 200 mg capsules
Antifibrinolytics:					
Tranexamic Acid	12	PO	Yes	Off-label for adult: 1 g PO bid (0.25 g bid to 1.5 g tid) Off-label for pediatric individuals: 20 mg/kg PO bid (10 mg/kg bid to 25 mg/kg tid)	650 mg tablets

Treatments used for acute episodes of hereditary angioedema (HAE):

	Laryngeal attack	Abdominal attack	Cutaneous attack	
			Extremities, trunk	Face, neck
C1INH concentrate (plasma derived or recombinant) given intravenously	Yes	Yes	Yes, unless swelling is extensively mild and not causing disability	Yes
Kalbitor (ecallantide)	Yes	Yes	Yes, unless extensively mild	Yes
Icatibant	Yes	Yes	Yes, unless extensively mild	Yes
Plasma (solvent / detergent treated or fresh frozen)	Yes, if first line therapies are not available	Yes, if first line therapies are not available	Yes, if severe and first line therapies are not available	Yes
Intubation, transfer to ICU	Yes, consider early intubation if above agents are not available	Not applicable	Not applicable	May be necessary if attack spreads to involve upper airway
Wait and see for spontaneous resolution	Not sufficient	Not recommended unless symptoms are mild and first line therapies are not available	Acceptable if mild	Not sufficient because angioedema can spread to involve airway

PHARMACY COVERAGE GUIDELINE

HEREDITARY ANGIOEDEMA MEDICATION THERAPY

Choices of prophylactic agent for hereditary angioedema (HAE) in specific patient groups

Patient population	Preferred agents	Alternate agents	Agents to avoid	Other notes
Pre-pubertal children (male and female)	Plasma-derived C1-INH* (Cinryze, Haegarda)	Tranexamic acid (less effective but may be sufficient for mild disease)	Androgens¶	Berotralstat not studied or approved for children under 12 years of age
Adult women not considering pregnancy and post-pubertal girls	Plasma-derived C1-INH* (Cinryze, Haegarda) Lanadelumab (Takhzyro) Berotralstat (Orladeyo)	Tranexamic acid (less effective but may be sufficient for mild disease)	Androgens (multiple side effects and virilization)	
Adult men and post-pubertal boys	Plasma-derived C1-INH* (Cinryze, Haegarda) Lanadelumab Berotralstat	Tranexamic acid (less effective but may be sufficient for mild disease) Androgens (multiple side effects but virilization less of an issue for men)		
Pregnant and lactating women	Plasma-derived C1-INH* (Cinryze, Haegarda) – have the most safety data	Tranexamic acid (less effective but history of safe use)	Androgens Δ	Lanadelumab and berotralstat not recommended because they have not been studied in pregnancy

The choice of which long-term prophylactic agent to use is influenced both by patient characteristics (age, gender, pregnancy/lactation), as shown in the table, as well as regulatory requirements in different countries.
* Plasma-derived C1-INH can be given subcutaneously or intravenously. Subcutaneous is more convenient and appears to be more effective based on preliminary evidence.
¶ Androgens are contraindicated in pre-pubertal children because they can cause premature closure of the growth plates.
Δ Androgens are avoided in pregnancy because they can result in virilization of female fetuses, although if a woman with HAE is carrying a male fetus, androgens have been successfully used with supervision by an endocrinologist.

Resources:

Berinert (C1 esterase inhibitor, human) product information, revised by CSL Behring GmbH 09-2021, at DailyMed http://dailymed.nlm.nih.gov. Accessed September 06, 2023.

Cinryze (C1 esterase inhibitor, human) product information, revised by Takeda Pharmaceuticals America, Inc. 02-2023, at DailyMed http://dailymed.nlm.nih.gov. Accessed September 06, 2023.

Haegarda (C1 esterase inhibitor, human) product information, revised by CSL Behring GmbH 01-2022, at DailyMed http://dailymed.nlm.nih.gov. Accessed September 06, 2023.

Ruconest (C1 esterase inhibitor, recombinant) product information, revised by Bioconnection B.V., Inc. 03-2018, at DailyMed http://dailymed.nlm.nih.gov. Accessed September 06, 2023.

Firazyr (icatibant) product information, revised by Takeda Pharmaceuticals America, Inc. 10-2021, at DailyMed http://dailymed.nlm.nih.gov. Accessed September 06, 2023.

Sajazir (icatibant) product information, revised by Cycle Pharmaceuticals Ltd-UK. 05-2022, at DailyMed http://dailymed.nlm.nih.gov. Accessed September 06, 2023.

Icatibant product information, revised by Aotec Corp. 10-2022, at DailyMed http://dailymed.nlm.nih.gov. Accessed September 06, 2023.

Kalbitor (ecallantide) product information, revised by Takeda Pharmaceuticals America, Inc. 11-2021, at DailyMed http://dailymed.nlm.nih.gov. Accessed September 06, 2023.

Orladeyo (berotralstat) capsule product information, revised by BioCryst Pharmaceuticals, Inc. 03-2022, at DailyMed http://dailymed.nlm.nih.gov. Accessed September 06, 2023.

Takhzyro (lanadelumab-flyo) product information, revised by Takeda Pharmaceuticals America. 02-2023, at DailyMed http://dailymed.nlm.nih.gov. Accessed September 06, 2023.

Zuraw B, Farkas H. Hereditary angioedema (due to C1 inhibitor deficiency): Pathogenesis and diagnosis. In: UpToDate, Saini S, Feldweg AM (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Literature current through August 2023. Topic last updated February 08, 2022. Accessed September 06, 2023.

Zuraw B, Farkas H. Hereditary angioedema: Epidemiology, clinical manifestations, exacerbating factors, and prognosis. In: UpToDate, Saini S, Feldweg AM (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Literature current through August 2023. Topic last updated August 15, 2022. Accessed September 06, 2023.

Zuraw B, Bork K. Hereditary angioedema with normal C1 inhibitor. In: UpToDate, Saini S, Feldweg AM (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Literature current through August 2023. Topic last updated October 11, 2021. Accessed September 06, 2023.

Zuraw B, Farkas H. Hereditary angioedema: Acute treatment of angioedema attacks. In: UpToDate, Saini S, Feldweg AM (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Literature current through August 2023. Topic last updated May 09, 2023. Accessed September 06, 2023.

Zuraw B, Farkas H. Hereditary angioedema: Short-term prophylaxis before procedures or stressful events to prevent angioedema episodes. In: UpToDate, Saini S, Feldweg AM (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Literature current through August 2023. Topic last updated June 29, 2023. Accessed September 06, 2023.

Zuraw B, Farkas H. Hereditary angioedema (due to C1 inhibitor deficiency): General care and long-term prophylaxis. In: UpToDate, Saini S, Feldweg AM (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Literature current through August 2023.Topic last updated June 29, 2023. Accessed September 06, 2023.

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 2021;9:132-50. Accessed January 20, 2021. Re-evaluated September 08, 2023

Maurer M, Magerl M, Betschel S, et al.: The international WAO/EAACI guideline for the management of hereditary angioedema – The 2021 revision and update. Maurer et al. World Allergy Organization Journal (2022) 15:100627 http://doi.org/10.1016/j.waojou.2022.100627. Accessed October 10, 2023.

Betschel S, Badiou J, Binkley K, et al.: The International/Canadian Hereditary Angioedema Guideline. Allergy Asthma Clin Immunol (2019) 15:72 https://doi.org/10.1186/s13223-019-0376-8. Accessed October 10, 2023.