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Policy Number: C21463-A

Hereditary Angioedema Agents

PRODUCTS AFFECTED

Firazyr (icatibant acetate), icatibant acetate, Sajazir (icatibant acetate), Berinert (C1 esterase inhibitor (human)), Ruconest (C1 esterase inhibitor (recombinant)), Kalbitor (ecallantide), Cinryze (C1 esterase inhibitor (human)), Haegarda (C1 esterase inhibitor (human)), Takhzyro (lanadelumab)

COVERAGE POLICY

Coverage for services, procedures, medical devices, and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.
This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Hereditary angioedema (HAE)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case- by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review.

FOR ALL INDICATIONS:

1. Documentation of HAE diagnosis and subtype confirmed by ONE of the following [DOCUMENTATION REQUIRED]:
   (a) TYPE 1 OR 2 HAE; Presence of a mutation in the C1-INH gene altering protein synthesis and/or function

OR

(b) BOTH of the following: (documentation of TWO (2) separate low measurements for each test defined as below the testing laboratory's lower limit of the normal range):

(i) Low serum complement factor 4 (C4) level (< 14mg/dL) AND

(ii) Low C1 inhibitor (C1-INH) level (C1-INH < 19.9 mg/dL), OR Low C1-INH functional level (functional C1-INH < 72%)

OR

(c) Documented diagnosis HAE with normal C1 inhibitor levels as evidenced by normal C4 level and normal C1-INH levels AND any of the following:

(i) Episodic angioedema affecting characteristic organs, without urticaria

(ii) A documented family history of angioedema

(iii) Presence of a FXII mutation (or possibly an angiopoietin-1 or plasminogen mutation) associated with the disease

AND

2. Documentation of baseline record of the following aspects of HAE attacks: Severity, duration and functional abilities in order to evaluate efficacy during re-authorization [DOCUMENTATION REQUIRED]
AND
3. Prescriber attests that all other causes and potentially treatable triggers of HAE attacks (i.e., stress, trauma, infection, etc.) have been identified and optimally managed
AND
4. Prescriber attests concurrent therapies that may exacerbate HAE, have been evaluated and discontinued as appropriate, including: Estrogen-containing medications [e.g. hormone replacement therapy, contraceptives], ACE-inhibitor (ACEI), Angiotensin II receptor blockers
AND
5. IF THIS IS A NON-FORMULARY/NON-PREFERRED PRODUCT: Documentation of trial/failure of, or intolerance to, a majority (not more than 3) of the preferred/formulary alternatives for the given diagnosis. Submit documentation including medication(s) tried, dates of trial(s) and reason for treatment failure(s).

A. TREATMENT OF ACUTE HEREDITARY ANGIOEDEMA ATTACKS (Firazyr, Berinert, Ruconest, Kalbitor):

1. Prescriber attests [or documentation provided supports] that requested medication is prescribed for ACUTE treatment of acute abdominal, facial, or laryngeal HAE attacks associated with HAE (not for routine prophylaxis)
AND
2. Member is NOT concurrently on, or using in combination with, other approved treatments for ACUTE HAE attacks
AND
3. Prescriber provides member's current history of acute attacks and documented evaluation for eligibility for prophylaxis therapy
AND
4. For Berinert [C1 esterase inhibitor, (human)] requests and Ruconest [C1 esterase inhibitor (recombinant)]: Documentation of patient weight taken within the previous 30 days
AND
5. For Kalbitor (ecallantide) and Ruconest (C1 esterase inhibitor [recombinant]) requests:
(a) FOR ADULT MEMBERS ≥18 YEARS OF AGE): Documentation of trial, failure, or contraindication to icatibant (Firazyr)
OR
(b) FOR CHILDREN AGES 5-17 YEARS: Documentation of trial, failure, or contraindication to Berinert (C1 esterase inhibitor, human)

B. PROPHYLAXIS FOR HEREDITARY ANGIOEDEMA (Cinryze, Haegarda, Takhzyro):

1. Prescriber attests [or documentation provided supports] that requested medication is prescribed for routine angioedema prophylaxis in patients with HAE (not for acute use)
   AND
2. Member is NOT concurrently on, or using in combination with, other approved treatments for prophylaxis against HAE attacks
   AND
3. For Haegarda [C1 esterase inhibitor, (human)] requests:
   (a)Documentation of member weight taken within the previous 30 days
   AND
   (b) FOR ADULT PATIENTS ≥18 YEARS OF AGE): Documentation of trial, failure, or contraindication to Takhzyro (lanidalimab)
   OR
   (c) FOR CHILDREN AGES 6-17 YEARS: Documentation of trial, failure, or contraindication to Cinryze (C1 esterase inhibitor, human)

CONTINUATION OF THERAPY:

FOR ALL INDICATIONS:

1. Subsequent authorizations require re-assessment of treatment regimen/plan, an evaluation of the frequency of HAE attacks and complete clinical review of member's condition to determine if continuation of treatment with requested treatment is medically necessary.

A. FOR TREATMENT OF ACUTE HEREDIATRY ANGIOEDEMA ATTACKS
   1. Documentation of significant improvement in the following aspects of HAE attacks have been achieved: Severity, Duration or Clinical documentation of functional improvement [DOCUMENTATION REQUIRED]
      AND
   2. Member is NOT concurrently on, or using in combination with, other approved treatments for ACUTE HAE attacks
      AND
   3. (a) IF MEMBER IS CONCURRENTLY ON PROPHYLAXIS MEDICATION FOR HAE: Adherence to prophylactic therapy for HAE (with antifibrinolytics, attenuated androgens, or plasma derived C1 inhibitor replacement therapy) OR prescriber attestation that member no longer requires prophylactic therapy NOTE: Adherence to prescribed prophylactic therapy for HAE must be confirmed by member's prescription claims. If member is new to Molina and does not have a prescription claims history, Prescriber certifies that the member has been adherent to the prescribed prophylactic therapy.
      OR
      (b) IF MEMBER IS NOT CONCURRENTLY ON A PROPHYLAXIS MEDICATION FOR HAE: Prescriber attests that member has had an annual evaluation for the need for long-term prophylaxis therapy

B. FOR PROPHYLAXIS FOR HEREDITARY ANGIOEDEMA (HAE):
   1. Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history (review Rx history for compliance)
      AND
   2. Documentation of significant improvement in the following aspects of HAE attacks have been achieved and sustained: reduction in frequency of HAE attacks or clinical documentation of functional improvement. [DOCUMENTATION REQUIRED]
      INFORMATIONAL NOTE: The goal of long-term therapy is to decrease or eliminate attacks, and success should be measured by this clinical outcome rather than by laboratory parameters.
      AND

3. Prescriber attests that member has had an annual evaluation for the continued need for long- term prophylaxis therapy
   AND
4. Member is NOT concurrently on, or using in combination with, other approved treatments for prophylaxis against HAE attacks
   AND
5. For Takhzyro: Documentation of frequency of attacks since starting Takhzyro therapy
   a. If ZERO attacks have occurred within 6 months since starting Takhzyro therapy, documentation of member evaluation for extended dosing interval of 300mg every 4 weeks
      OR
   b. If documentation provided show member is not attack free- must demonstrate improvement from baseline in severity, duration or frequency of attacks

DURATION OF APPROVAL:
Initial authorization: 6 months, Continuation of therapy: 12 months

PRESCRIBER REQUIREMENTS:
Prescribed by, or in consultation with, a board-certified immunologist, allergist, hematologist, or physician experienced in the treatment of C1-esterase inhibitor deficiency. Submit consultation notes if applicable. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:
Firazyr (icatibant acetate), icatibant acetate, Sajazir: 18 years of age and older
Berinert (C1 esterase inhibitor (human)): 5 years of age and older
Ruconest (C1 esterase inhibitor (recombinant)): 13 years of age and older
Kalbitor (ecallantide):12 years of age and older
Cinryze (C1 esterase inhibitor (human)): 6 years of age and older
Haegarda (C1 esterase inhibitor (human)): 6 years of age and older
Takhyzyro (lanadelumab): 12 years of age and older

QUANTITY:
Firazyr, icatibant acetate, Sajazir: Maximum of 3 injections (90 mg or 9 mL) in 24 hours if response is inadequate or symptoms recur. May authorize up to a sufficient quantity for member to have a cumulative amount on-hand to treat up to 2 acute attacks per month [6 syringes per 30 days]

Berinert: Adults: 20 International Units per kg body weight per dose, Children ≥5 years and Adolescents: IV: 20 units/kg
May authorize up to a sufficient quantity for member to have a cumulative amount on-hand to treat up to 2 acute attacks per month [*5,000 unit (10 vials) per 30 days]

Ruconest: 50 IU per kg with a maximum of 4,200 units (2 vials) to be administered as a slow intravenous injection over approximately 5 minutes. No more than two doses should be administered within a 24 hour period. May authorize up to a sufficient quantity for member to have a cumulative amount on-hand to treat up to 2 acute attacks per month [8 vials per 30 days]
Body weight < 84 kg: 50 IU/kg Body weight ≥ 84 kg: 4200 IU (2 vials)

Kalbitor: 30 mg (3 mL) administered subcutaneously in three 10 mg (1 mL) injections. If the attack persists, an additional dose of 30 mg may be administered within a 24-hour period. Must be administered by a health care provider. May authorize up to a sufficient quantity for member to have a cumulative amount on-hand to treat up to 2 acute attacks per month.

Cinryze: Adults and adolescents (12 years old and above): Routine prophylaxis against HAE attacks:

Administer 1,000 units Intravenous (IV) every 3 or 4 days. For members who have not responded adequately to 1,000 U of Cinryze every 3 or 4 days, doses up to 2,500 U (not exceeding 100 U/kg) every 3 or 4 days may be considered based on individual member response. Children (6 to 11 years old): Routine prophylaxis against HAE attacks 500 Units Intravenous every 3 or 4 days**Doses up to 1,000 U every 3 to 4 days may be considered based on individual patient response.

Haegarda: 60 International Units (IU) per kg body weight by subcutaneous (S.C.) injection twice weekly (every 3 or 4 days).

Takhzyro: 300 mg every 2 weeks. A dosing interval of 300 mg every 4 weeks is also effective and may be considered if the patient is well-controlled (e.g., attack free) for more than 6 months.

Maximum Quantity Limits –
Firazyr, icatibant acetate, Sajazir: 6 syringes/ 30 days
Berinert: 10 vials (5000 unit)/30 days
Ruconest: 8 vials (16,800 units)/30 days
Kalbitor: 12 vials/30 days
Cinryze: 2,500 U (not to exceed 100 U/kg) every 3 or 4 days Haegarda: maximum of 2 doses per week and 8 doses per 28 days Doses less than 2,000 IU, must use (1) 2,000 IU vial, Doses greater than 2,000IU but less than 3,000IU, must use (1) 3,000IU vial, Doses greater than 3,000IU but less than 4,000IU, must use (2) 2,000IU vials, Doses greater than 4,000IU but less than 5,000IU must use (1) 2,000IU vial and (1) 3,000IU vial, Doses greater than 5,000 but less than 6,000IU can use either (3) 2,000IU vial OR (2) 3,000IU vial, Doses greater than 6,00IU but less than 8,000IU must use (2) 3,000IU vials AND (1) 2,000IU vial, Doses greater than 8,000IU but less than 9,000IU must use (3) 3,000IU vials, Doses greater than 9,000IU, must utilize vial optimization
Takhzyro: 2 vials (4 mL)/ 28 days - if attack free for 6 months- 1 vial (2ml) per 28 days

PLACE OF ADMINISTRATION:
Berinert (C1 esterase inhibitor (human)), Ruconest (C1-inhibitor (recombinant)), Cinryze (C1 esterase inhibitor (human)): The recommendation is that infused medications in this policy will be for pharmacy or medical benefit coverage administered in a place of service that is a non-hospital facility-based location as per the Molina Health Care Site of Care program.

Kalbitor (ecallantide): The recommendation is that injectable medications in this policy will be for pharmacy or medical benefit coverage and the subcutaneous injectable products administered in a place of service that is a non-hospital facility-based location as per the Molina Health Care Site of Care program.

Haegarda (C1 esterase inhibitor (human)), Takhzyro (lanadelumab), Firazyr (Icatibant acetate): The recommendation is that injectable medications in this policy will be for pharmacy benefit coverage and patient self-administered as per the Molina Health Care Site of Care program.

Note: Site of Care Utilization Management Policy applies for Berinert, Ruconest, Cinryze, Kalbitor, Haegarda, Takhzyro, and Firazyr. For information on site of care, see
Specialty Medication Administration Site of Care Coverage Criteria (molinamarketplace.com)

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Subcutaneous Injection, Intravenous

DRUG CLASS:
Bradykinin B2 Receptor Antagonists, Plasma Kallikrein Inhibitor, C1-Inhibitor

FDA-APPROVED USES:

Berinert: for the treatment of acute abdominal, facial, or laryngeal hereditary angioedema (HAE) attacks in adult and pediatric patients.

Ruconest: for the treatment of acute attacks in adult and adolescent patients with hereditary angioedema (HAE).
Limitation of Use: Effectiveness was not established in HAE patients with laryngeal attacks.

Kalbitor: for treatment of acute attacks of hereditary angioedema (HAE) in patients 12 years of age and older.

Firazyr, icatibant acetate, Sajazir: for the treatment of acute attacks of hereditary angioedema (HAE) in adults 18 years of age and older.

Cinryze: for routine prophylaxis against angioedema attacks in adults, adolescents and pediatric patients (6years old and above) with Hereditary Angioedema (HAE).

Haegarda: for routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks inpatients 6 years of age and older

Takhzyro: for prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older.

COMPENDIAL APPROVED OFF-LABELED USES:
Hereditary angioedema with normal C1 inhibitor levels

APPENDIX

APPENDIX:
THERAPIES FOR HEREDITARY ANGIOEDEMA

	FDA INDICATION	DOSE	MECHANISM OF ACTION	AGE INDICATIONS
Berinert® C1 esterase inhibitor (human)	ACUTE TREATMENT	20 units/kg IV	C1-inhibitor [human]	5 AND OLDER
Ruconest® C1-inhibitor (recombinant)	ACUTE TREATMENT	50 units/kg IV (max. 4,200 units)	C1-inhibitor [recombinant]	13 AND OLDER
Kalbitor® ecallantide	ACUTE TREATMENT	30 mg SC (as three 10 mg/ml injections)	Plasma kallikrein inhibitor	12 AND OLDER
Firazyr® Icatibant acetate	ACUTE TREATMENT	30 mg SC	Bradykinin receptor antagonist	18 AND OLDER
Cinryze® C1 esterase inhibitor (human)	PROPHYLAXIS	1,000 units via IV route every 3-4 days	C1-inhibitor [human]	6 AND OLDER
Haegarda® C1 esterase inhibitor (human)	PROPHYLAXIS	60 units/kg SC every 3-4 days	C1-inhibitor [human]	6 AND OLDER
Takhzyro® lanadelumab	PROPHYLAXIS	300 mg SC every 2 weeks	Plasma kallikrein inhibitor	12 AND OLDER

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Hereditary Angioedema (HAE)

A rare genetic disorder of recurrent attacks of localized subcutaneous or mucosal swelling that affects 1 in 10,000 to 1 in 50,000 individuals in the United States. Attack frequency varies from a few days to decades between attacks and severity ranges from mild to more severe laryngeal edema causing airway obstruction and fatal asphyxiation. Formal diagnosis is often significantly delayed following onset of symptoms and misdiagnosis or medical mismanagement is not uncommon. The two most common forms of HAE (Types I and II) may be managed with prophylaxis or acute treatment depending on attack frequency, severity, and drug tolerability.

HAE-1/2 is a rare autosomal dominant condition affecting an estimated 1 in 50,000 individuals, although this may vary in different regions. HAE-1/2 is caused by one of more than 450 different mutations in the SERPING1 gene, which codes for C1-INH [40]. In approximately 20–25% of patients, a de novo mutation of SERPING1 is responsible for the disease. C1-INH is a serine protease inhibitor (SERPIN) and the major inhibitor of several complement proteases (C1r, C1s, and mannose-binding lectin–associated serine protease [MASP] 1 and 2) and contact-system proteases (plasma kallikrein and coagulation factor XIIa) as well as a relatively minor inhibitor of the fibrinolytic protease plasmin. The primary mediator of swelling in HAE-1/2 is bradykinin [28]. Bradykinin is a low molecular weight nonapeptide, which is generated when active plasma kallikrein cleaves high molecular weight kininogen (HMWK). Bradykinin is rapidly metabolized by endogenous metalloproteases including angiotensin-converting enzyme (ACE). Plasma kallikrein is activated from its inactive zymogen prekallikrein by the protease factor XII, which can easily autoactivate upon contact with negatively charged surfaces. Both, plasma kallikrein and factor XII are inhibited by C1-INH. Increased vascular permeability induced by the liberation of bradykinin in angioedema is primarily mediated through the bradykinin B2 receptor.

HAE with normal C1 inhibitor

HAE with normal C1-INH (HAE nC1-INH) is a very rare disease. Its clinical appearance largely resembles that of HAE-1/2. In a subgroup of patients, HAE nC1-INH is associated with mutations of the factor XII (FXII-HAE) gene. Recently, two new mutations in - (ANGPT1) and plasminogen (PLG) were reported in HAE nC1-INH. However, in most patients with HAE nC1-INH, no gene mutation can be found, and the pathogenesis remains to be characterized in detail. However, there is clinical evidence that bradykinin may play a major role in some types of HAE nC1-INH, primarily in patients with a FXII-mutation [52–54]. Although HAE nC1-INH shares some clinical features and, possibly, therapeutic options with HAE-1/2, this guideline is for HAE-1/2.

C1-Inh Deficiency	Inherited	HAE-1 hereditary angioedema due to C1-Inhibitor deficiency, HAE-2 hereditary angioedema due to C1-Inhibitor dysfunction
	Acquired	AAE-C1-INH acquired angioedema due to C1-Inhibitor deficiency
C1 Inh- Normal	Inherited	HAE nC1-INH hereditary angioedema with normal C1-Inhibitor levels, either due to a mutation in FXII, ANGPTI, PLG or unknown (HAE-FXII, HAE-ANGPTI, HAE-PLG, HAE-UNK),
	Acquired	ACEI-AE angiotensin converting enzyme inhibitor-induced angioedema

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of these medications are considered experimental/investigational and therefore, will follow Molina's Off- Label policy.

Berinert (C1 esterase inhibitor (human)): contraindicated in individuals who have experienced life-threatening hypersensitivity reactions, including anaphylaxis, to C1 esterase inhibitor preparations
Ruconest (C1 esterase inhibitor (recombinant)) is contraindicated in patients with a history of allergy to rabbits or rabbit-derived products. RUCONEST is contraindicated in patients with a history of life-threatening immediate hypersensitivity reactions to C1 esterase inhibitor preparations, including anaphylaxis.
Kalbitor (ecallantide): Boxed warning. Anaphylaxis has been reported after administration of KALBITOR. Because of the risk of anaphylaxis, KALBITOR should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema. Healthcare professionals should be aware of the similarity of symptoms between hypersensitivity reactions and hereditary angioedema and patients should be monitored closely. Do not administer KALBITOR to patients with known clinical hypersensitivity to KALBITOR.
Cinryze (C1 esterase inhibitor (human)): contraindicated in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product.
Haegarda (C1 esterase inhibitor (human)): contraindicated in individuals who have experienced life-threatening hypersensitivity reactions, including anaphylaxis, to C1-INH preparations or its excipients
Firazyr, Sajazir (incatibant acetate): No labeled contraindications

OTHER SPECIAL CONSIDERATIONS:

Takhzyro is distributed by a limited network of 5 specialty pharmacies: Accredo, Briova, CVS Caremark, OptionCare, Orsini.
The efficacy of Takhzyro for the prevention of angioedema attacks in members 12 years of age and older with Type I or II HAE was demonstrated in a multicenter, randomized, double-blind, placebo controlled parallel- group study. The study included 125 adult and adolescent members with HAE who experienced at least one investigator-confirmed attack per 4 weeks during the run-in period. Members were randomized into 1 of 4 parallel treatment arms for the 26-week treatment period. All Takhzyro treatment arms produced clinically meaningful and statistically significant reductions in the mean HAE attack rate compared to placebo across all primary and secondary endpoints in the intent-to- treat (ITT) population. An open-label, long-term safety and efficacy study is ongoing and expected to complete in November 2019. The HELP study also collected exploratory endpoints that included the percentage of members who were attack free for the entire 26-week treatment period. The percentage of attack-free members for the entire 26-week treatment period is listed in the chart above. The attack-free rate was used to determine whether and how members could step down in dosing frequency. For members on the 300mg every 2 weeks, the attack-free rate increased to 77% when measured from days 70-182 on treatment.
The lower attack-free rate seen in the first 6 months was likely due to the long half-life of Takhzyro and that members did not reach steady state until around 70 days. There have been no head-to-head comparisons among any of the products for HAE. According to the individual product prescribing information, the reduction in monthly attack rate versus placebo of all three products remain comparable

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
J0597	Injection, C-1 esterase inhibitor (human), Berinert, 10 units
J0598	Injection, C-1 esterase inhibitor (human), Cinryze 10 units
J0596	Injection, c1 esterase inhibitor (recombinant), Ruconest, 10 units

J1290	Injection, ecallantide, 1 mg
J0593	Injection, lanadelumab-flyo, 1 mg

AVAILABLE DOSAGE FORMS:
Firazyr SOLN 30MG/3ML, single use pre-filled syringe, Box of 1
Firazyr SOLN 30MG/3ML, single use pre-filled syringe, Box of 3
Berinert KIT 500UNIT/10mL
Cinryze 500 Units (lyophilized) in an 8 mL vial
Haegarda SOLR single-dose vials containing 2000 or 3000 International Units (IU)
Ruconest single-use 2100 Unit vial
Takhzyro 300 mg/2 mL (150 mg/mL) vial.
Icatibant Acetate SOLN 30MG/3ML
Sajazir SOLN 30MG/3ML

REFERENCES

1. Firazyr® [prescribing information]. Lexington, MA: Shire Orphan Therapies Inc; October 2021.
2. Craig T, Pursun EA, Bork K, et al. WAO guideline for the management of hereditary angioedema. WAO Journal.2012;5:182-199.
3. Berinert [package insert]. Kankakee, IL; CSL Behring LLC; October 2021
4. Bygum A, Andersen KE, Mikkelsen CS. Self-administration of intravenous C1-inhibitortherapy for hereditary angioedema and associated quality of life benefits. Eur J Dermatol.Mar-Apr 2009;19(2):147-151.
5. Bowen T, Cicardi M, Farkas H, et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Allergy Asthma Clin Immunol. 2010;6(1):24.
6. Gompels MM, Lock RJ, Abinun M, et al. C1 inhibitor deficiency: consensus document. ClinExp Immunol. 2005;139(3):379.
7. Haegarda® [prescribing information]. King of Prussia, PA: CSL BehringGmbH. January 2022
8. Craig TJ, Schneider LC, MacGinnitie AJ.Plasma-derived C1-INH for managing hereditary angioedema in pediatric patients: A systematic review. Pediatr Allergy Immunol.2015 Sep;26(6):537-44.
9. Agostoni, Angelo, et al.“"Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond”" Journal of Allergy and Clinical Immunology 114.3 (2004): S51- S131.
10. Weiler CR, van Dellen RG. Genetic test indications and interpretations in patients with hereditary angioedema. Mayo Clin Proc. 2006Jul;81(7):958-72
11. Cinryze® [prescribing information]. New York, NY: ViroPharma Biologics; January 2021
12. TAKHZYRO [prescribing information]. Lexington, MA: Dyax Corp;.February 2022
13. Ruconest® [prescribing information]. Raleigh, NC: Salix Pharmaceuticals, Inc.; April 2020
14. Genetic test indications and interpretations in members with hereditary angioedema. WeilerCR, van Dellen RG. Mayo Clin Proc. 2006 Jul;81(7):958-72
15. Kalbitor® [prescribing information]. Cambridge, MA: Dyax Corporation; December 2020
16. Bork K, Bernstein JA, Machnig T, Craig TJ. Efficacy of different medical therapies for the treatment of acute laryngeal attacks of hereditary angioedema due to C1-esterase inhibitor deficiency. J Emerg Med. 2016 Apr;50(4):567-580.

17. Vitrat-Hincky V, Gompel A, Dumestre-Perard C, Boccon-Gibod I, Drouet C, Cesbron JY, et al. Type III hereditary angio-oedema: clinical and biological features in a French cohort. Allergy 2010;65:1331-6, IIb.
18. Bork K. Hereditary angioedema with normal C1 inhibitor activity including hereditary angioedema with coagulation factor XII gene mutations. Immunol Allergy Clin North Am2006;26:709-24, III.
19. Maurer M, Magerl M, Ansotegui I, et al. The International WAO/EAACI guideline for themanagement of hereditary angioedema – the 2017 revision and update. World Allergy Organization Journal. 2018;11(5).
20. Sajazir (icatibant acetate) injection [package insert]. Cambridge, UK: Cipla, Ltd.; June 2021.

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Products Affected Required Medical Information Continuation of Therapy Age Restrictions Quantity FDA-Approved uses Contraindications/Exclusions/Discontinuation Available Dosage Forms References	Q3 2022
Q2 2022 Established tracking in new format	Historical changes on file