Clinical Policy Title:	ecallantide
Policy Number:	RxA.185
Drug(s) Applied:	Kalbitor®
Original Policy Date:	02/07/2020
Last Review Date:	06/10/2021
Line of Business Policy Applies to:	All lines of business

Background

Ecallantide (Kalbitor®) is a plasma kallikrein inhibitor. It is indicated for treatment of acute attacks of hereditary angioedema (HAE) in patients 12 years of age and older.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
ecallantide (Kalbitor®)	Treatment of acute HAE attacks	30 mg administered SC in three 10 mg (1 mL) injections; if attack persists, an additional dose of 30 mg may be administered within a 24-hour period.	60 mg/24 hours

Dosage Forms

- Vial with solution for injection: 10 mg/mL.

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of prescriber samples does not guarantee coverage under the provisions of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Hereditary Angioedema (must meet all)**:**

1. Diagnosis of HAE confirmed by one of the following (a or b):
   a. Low C4 level and low C1-INH antigenic or functional level (*see Appendix D*);
   b. Normal C4 level and normal C1-INH levels, and either of the following (i or ii):
      i. History of recurrent angioedema;
      ii. Family history of angioedema;
2. Prescribed by or in consultation with a/an hematologist, allergist, or immunologist;
3. Age is 12 years or older;
4. Prescribed for treatment of acute HAE attacks (not prophylaxis);

5. Member is not using Kalbitor® in combination with another FDA-approved product for treatment of acute HAE attacks (e.g., Berinert®, Ruconest®, Firazyr®, Cinryze ®);
6. Dose does not exceed 30 mg (1 carton [3 vials]) per dose, with up to 2 doses administered in a 24-hour period.

Approval Duration
Commercial: 6 months (up to 4 doses per month)
Medicaid: 12 months (up to 4 doses per month)

II. Continued Therapy Approval

A. Hereditary Angioedema (must meet all)**:**

1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;
3. Member is not using Kalbitor® in combination with another FDA-approved product for treatment of acute HAE attacks (e.g., Berinert®, Ruconest®, Firazyr®, Cinryze ®etc);
4. If request is for a dose increase, new dose does not exceed 30 mg (1 carton [3 vials]) per dose, with up to 2 doses administered in a 24-hour period.

Approval Duration
Commercial: 6 months (up to 4 doses per month)
Medicaid: 12 months (up to 4 doses per month)

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
C1-INH: C1 inhibitor
FDA: Food and Drug Administration
HAE: hereditary angioedema

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/Maximum Dose
Berinert®	20 IU/kg IV	20 IU/kg IV
Cinryze®	1,000 units IV over at least 10 minutes every 3 to 4 days. For patients who do not respond adequately, doses up to 2,500 units (Max: 100 units/kg) every 3 to 4 days may be considered.	2,500 units (Max: 100 units/kg) IV every 3 days
Haegarda®	60 IU/kg SC twice weekly (every 3 or 4 days).	60 IU/kg SC every 3 days
Ruconest®	50 /kg/dose IV	50 IU/kg/dose (Max: 4200 IU/dose)
icatibant (Firazyr®)	30 mg SC/ dose	90 mg/24 hours SC
Takhzyro®	300 mg SC every 2 weeks	300 mg SC every 2 weeks

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Do not administer Kalbitor® to a patient who has known clinical hypersensitivity to Kalbitor®.

- Boxed Warning(s):
  - Due to the risk for 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 hypersensitivity to Kalbitor®.

APPENDIX D: General Information

- Diagnosis of HAE:
  - HAE is classified as Type -1 HAE – due to C1-INH deficiency, Type -2 HAE – due to C1-INH dysfunction and three rare conditions which are associated with mutations.
  - In both Type 1 (~85% of cases) and Type II (~15% of cases), C4 levels are low. C1INH antigenic levels are low in Type I while C1-INH functional levels are low in Type II. Diagnosis of Type I and II can be confirmed with laboratory tests. Reference ranges for C4 and C1- INH levels can vary across laboratories (see below for examples); low values confirming diagnosis are those which are below the lower end of normal.

Laboratory Test & Reference Range	Mayo Clinic	Quest Diagnostics	LabCorp
C4	14-40 mg/dL	16-47 mg/dL	9-36 mg/dL
C1-INH, antigenic	19-37 mg/dL	21-39 mg/dL	21-39 mg/dL
C1-INH, functional	Normal: > 67% Equivocal: 41-67% Abnormal: < 41%	Normal: ≥ 68% Equivocal: 41-67% Abnormal: ≤ 40%	Normal: > 67% Equivocal: 41-67% Abnormal: < 41%

  - Cases may also presents with normal C4 and C1-INH levels. Some patients have an associated mutation in the FXII gene, while others have no identified genetic indicators. These types are very rare (number of cases unknown), and there are no laboratory tests to confirm the diagnosis. Instead, the diagnosis is clinical and supported by recurrent episodes of angioedema with a strong family history of angioedema.

References

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4. Craig T, Pursun E, Bork K, et al. WAO guideline for the management of hereditary angioedema. WAO Journal. 2012; 5: 182-199. Accessed February 19, 2021.
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Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy was reviewed: 1. Clinical Policy Title was updated. 2. Line of Business Policy Applies to was updated to all lines of business. 3. Commercial and Medicaid approval duration was updated. 4. Continued therapy criteria II.A.1. was rephrased to “Currently receiving medication that has been authorized by RxAdvance…” 5. References were updated.	07/01/2020	09/14/2020
Policy was reviewed: 1. APPENDIX B: Therapeutic Alternatives was added. 2. References were updated.	02/19/2021	06/10/2021