Reference number(s)
4230-A

Standard Medicare Part B Management Berinert

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Berinert	C1 esterase inhibitor [human]

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

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

Compendial Uses[5,7]

Short term preprocedural prophylaxis for HAE attacks

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

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- For initial authorization:
  - C1 inhibitor functional and antigenic protein levels
  - F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) pathogenic variant testing, if applicable
  - Chart notes confirming family history of angioedema and the member's angioedema was refractory to a trial of high-dose antihistamine therapy, if applicable
- For continuation of therapy for acute attacks, chart notes demonstrating a reduction in severity and/or duration of attacks

Coverage Criteria

Hereditary Angioedema (HAE)[1-14]

Preprocedural Prophylaxis

Authorization of 30 days may be granted for short-term preprocedural prophylaxis (i.e., prior to surgical or major dental procedures) when either of the following criteria is met at the time of diagnosis:

- Member has C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing and meets one of the following criteria:
  - C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test, or
  - Normal C1-INH antigenic level and a low C1-INH functional level (functional C1-INH less than 50% or C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test).
- Member has normal C1 inhibitor as confirmed by laboratory testing and meets one of the following criteria:
  - Member has an F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) pathogenic variant as confirmed by genetic testing, or
  - Member has a documented family history of angioedema and the member's angioedema was refractory to a trial of high-dose antihistamine therapy (i.e., cetirizine at 40 mg per day or the equivalent) for at least one month.

Acute Attacks

Authorization of 12 months may be granted for treatment of acute HAE attacks when either of the following criteria is met at the time of diagnosis:

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- Member has C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing and meets one of the following criteria:
    - C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test, or
    - Normal C1-INH antigenic level and a low C1-INH functional level (functional C1-INH less than 50% or C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test).
- Member has normal C1 inhibitor as confirmed by laboratory testing and meets one of the following criteria:
    - Member has an F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) pathogenic variant as confirmed by genetic testing, or
    - Member has a documented family history of angioedema and the member's angioedema was refractory to a trial of high-dose antihistamine therapy (i.e., cetirizine at 40 mg per day or the equivalent) for at least one month.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Preprocedural Prophylaxis

All members (including new members) requesting authorization for continued short-term preprocedural prophylaxis (i.e., prior to surgical or major dental procedures) must meet all requirements in the coverage criteria section.

Acute Attacks

Authorization of 12 months may be granted for continued treatment of acute HAE attacks when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy. Benefit is defined as reduction in severity and/or duration of acute attacks.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Berinert.

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- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- 2010 International consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema.
- Hereditary Angioedema International Working Group. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group.
- US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema.
- Hereditary Angioedema with Normal C1 Inhibitor: an Updated International Consensus Paper on Diagnosis, Pathophysiology, and Treatment. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2021 revision and update.
- International consensus on hereditary and acquired angioedema.
- Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group.
- Hereditary angioedema: beyond international consensus – The Canadian Society of Allergy and Clinical Immunology.
- International consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency.
- Diagnosis and screening of patients with hereditary angioedema in primary care.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Berinert are covered in addition to short-term preprocedural prophylaxis for HAE attacks.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the above diagnostic criteria can be found in the US HAEA Medical Advisory Board Guidelines for the Management of Hereditary Angioedema. When HAE is suspected based on the clinical presentation, the provider should test serum C4, C1INH antigenic level, and C1INH functional level. Low C4 and low C1INH antigenic or functional levels are consistent with a diagnosis of HAE with an abnormal C1INH.

When a diagnosis of HAE with normal C1INH is suspected, additional genetic tests for factor XII, plasminogen, angiopoietin-1, and kininogen pathogenic variants should be performed. If the genetic testing is unable to be performed or a known pathogenic variant is not found, the US HAEA guidelines indicate a positive family history of recurrent angioedema and a documented lack of efficacy of high-dose

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antihistamine therapy for at least 1 month or an interval expected to be associated with three or more attacks of angioedema, whichever is longer, can be used as clinical criteria to support the diagnosis. The understanding of the genetic pathogenic variants associated with HAE is evolving. Veronez et al have identified additional genetic pathogenic variants not mentioned in the US HAEA guidelines. There are five new genes associated with HAE and a normal C1-INH: ANGPT1 (angiopoietin-1), PLG (plasminogen), KNG1 (kininogen), MYOF (myoferlin), and HS3ST6 (heparan sulfate-glucosamine 3-O-sulfotransferase 6).

Support for using Berinert as short term preprocedural prophylaxis against HAE attacks can be found in the US HAEA guidelines. The goal of preprocedural prophylaxis is to reduce the likelihood of swelling in a patient undergoing a stressor or procedure likely to trigger an HAE attack. Acceptable short-term prophylaxis can be either Berinert or a course of anabolic androgen.

References

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