BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

ecallantide (Kalbitor®)

Policy # 00294
Original Effective Date: 03/21/2012
Current Effective Date: 07/16/2014

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of ecallantide (Kalbitor®)‡ † for the treatment of acute attacks of hereditary angioedema to be **eligible for coverage.**

Patient Selection Criteria
Coverage eligibility will be considered for the use of ecallantide (Kalbitor) for the treatment of acute attacks of hereditary angioedema when all of the following criteria are met:

- Patient has a diagnosis of hereditary angioedema as confirmed by appropriate lab test(s); and
- Patient's attacks are acute; and
- Patient is 12 years of age or older.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of ecallantide (Kalbitor) for the treatment of acute attacks of hereditary angioedema when patient selection criteria are not met to be **investigational.***

Background/Overview

Ecallantide (Kalbitor), an agent produced by recombinant DNA technology, is indicated for the treatment of acute attacks of hereditary angioedema (HAE) in patients aged ≥ 12 years. In HAE attacks, Kalbitor is given subcutaneously in three 10 mg (1 mL) injections; if an attack persists, an additional dose of 30 mg may be given in a 24 hour period. Kalbitor should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and HAE. Kalbitor is a reversible inhibitor of plasma kallikrein. It binds to plasma kallikrein and blocks its binding site, inhibiting the conversion of High Molecular Weight (HMW) kininogen to bradykinin. By directly inhibiting plasma kallikrein, Kalbitor reduces the conversion of HMW kininogen to bradykinin, and thereby treats symptoms of the disease during acute episodic HAE attacks. Bradykinin is a vasodilator which is believed by some to be responsible for the characteristic HAE symptoms of localized swelling, inflammation, and pain.

Hereditary Angioedema
Hereditary angioedema is a rare, autosomal dominant disease caused by a deficiency in functional C1 inhibitor. The disease is characterized by recurrent episodes of nonpruritic, nonpitting, subcutaneous or

ecallantide (Kalbitor®)

Policy # 00294
Original Effective Date: 03/21/2012
Current Effective Date: 07/16/2014

submucosal edema typically involving the arms, legs, hands, feet, bowels, genitalia, trunk, face, tongue or larynx. Its prevalence is not known but it is estimated to occur in approximately 1 case in 50,000 patients and it is believed to impact approximately 6000 patients in the US. Typically symptoms commence in childhood (often as early as two or three years of age) and worsen in adolescence and persist throughout life. There is a wide variation in the frequency and severity of attacks. Untreated patients typically experience attacks once weekly to twice weekly. However, some patients can have attacks approximately every three days and others may virtually never experience additional attacks. Clinical experience suggests that minor trauma and/or stress may precipitate attacks. Attacks usually are predictable, although different on an individual basis. A prodrome, such as a tingling sensation, may occur prior to an attack and approximately one-third of patients experience a nonpruritic, serpentine erythematous rash. The swelling typically slowly worsens over the first 24 hours and then gradually subsides over the next 48 to 72 hours. The most common sites of swelling are the arms, legs, hands, feet, and abdomen. Oropharyngeal swelling is less frequent but can be life-threatening when it occurs. Abdominal attacks may also happen, which can lead to severe abdominal pain, nausea and vomiting.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
The U.S. FDA approved Kalbitor on December 1, 2009 to treat sudden and potentially life-threatening fluid buildup that can occur in people with a rare genetic condition known as HAE. In March of 2014, the age for those approved to receive Kalbitor was lowered to 12 years.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The safety and efficacy of Kalbitor was assessed in two randomized, double-blind, placebo-controlled trials (EDEMA 4 and EDEMA 3) in 168 patients with HAE. Patients could have an HAE attack at any anatomic location, with at least one moderate or severe symptom, which was treated with Kalbitor 30 mg subcutaneously or placebo. A total of 143 unique patients participated (94 female, 123 Caucasian). The mean patient age was 36 years and there were 64 patients with abdominal attacks, 55 with peripheral attacks, and 24 with laryngeal attacks. In both studies the effects of Kalbitor were evaluated using the Mean Symptoms Complex Severity (MSCS) score and the Treatment Outcome Score (TOS). The MSCS is a point-in-time measure of symptom severity and the TOS measures symptom response to treatment. In the EDEMA 4 trial (n = 96), the changes in MSCS and TOS were statistically superior for Kalbitor compared with placebo at 4 hours and at 24 hours. Also, more patients given placebo (50%) required medical intervention to treat unresolved symptoms within 24 hours compared to the Kalbitor-treated group (33%). In EDEMA 3 (n = 72), patients given Kalbitor also had statistically superior changes in the MSCS and the TOS at four hours compared with placebo. Also, more patients in the placebo group (36%) required medical intervention to treat unresolved symptoms within 24 hours compared to the Kalbitor -treated group (14%).

ecallantide (Kalbitor®)

Policy # 00294
Original Effective Date: 03/21/2012
Current Effective Date: 07/16/2014

References

1. Kalbitor® [package insert]. Cambridge, MA; Dyax Corporation; March 2014.
2. Zuraw BL. Hereditary angioedema. *N Engl J Med*. 2008; 359:1027-1036.
3. Weis M. Clinical review of hereditary angioedema: diagnosis and management. *Postgrad Med*. 2009; 121(6):113-120.

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines (BCBSLAMPCG) are obtained from Current Procedural Terminology (CPT®)‡, copyright 2013 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J1290
ICD-9 Diagnosis	277.6
ICD-9 Procedure	No codes

Policy History

Original Effective Date: 03/21/2012
Current Effective Date: 07/16/2014
03/01/2012 Medical Policy Committee review
03/21/2012 Medical Policy Implementation Committee approval. New policy.
04/04/2013 Medical Policy Committee review
04/24/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/10/2014 Medical Policy Committee review
07/16/2014 Medical Policy Implementation Committee approval. Changed age from 16 to 12 years and older to coincide with change in package insert indication.
Next Scheduled Review Date: 07/2015

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

ecallantide (Kalbitor®)

Policy # 00294
Original Effective Date: 03/21/2012
Current Effective Date: 07/16/2014

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:
A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.