icatibant (Firazyr®, generics)

Policy # 00326
Original Effective Date: 03/21/2012
Current Effective Date: 11/11/2024

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 icatibant (Firazyr®, generics)‡ for the treatment of acute attacks of hereditary angioedema (HAE) to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility will be considered for the use of icatibant (Firazyr, generics) for the treatment of acute attacks of hereditary angioedema (HAE) when all of the following criteria are met:

- Patient has a diagnosis of hereditary angioedema based on meeting ONE of the following below:
    - 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 (i.e., 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); OR
    - Normal C1-INH as confirmed by laboratory testing and ONE of the following:
        - Presence of a genetic mutation associated with type 3 HAE (e.g., F12, angiopoietin-1, plasminogen, or kninogen-1 mutations); OR
        - Documented family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine for at least one month; AND

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- Requested drug is being used for the treatment of acute attacks of HAE; AND
- If the request is for brand Firazyr, patient has tried and failed (e.g., intolerance or inadequate response) GENERIC icatibant unless there is clinical evidence or patient history that suggests GENERIC icatibant will be ineffective or cause an adverse reaction to the patient.
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of brand Firazyr when the patient has not tried and failed GENERIC icatibant to be **not medically necessary.****

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 icatibant (Firazyr, generics) for the treatment of acute attacks of hereditary angioedema (HAE) when patient selection criteria are not met (except those denoted above as **not medically necessary****) to be **investigational.***

Background/Overview

Firazyr is a novel synthetic decapeptide that is indicated for the treatment of HAE attacks. Firazyr is a competitive bradykinin B2 receptor antagonist with an affinity similar to bradykinin. Bradykinin is a vasodilator which is likely responsible for the characteristic HAE symptoms of localized swelling, inflammation, and pain. By preventing the binding of bradykinin to its receptor, Firazyr treats the clinical symptoms of an acute HAE attack. The recommended dose for Firazyr is 30 mg administered subcutaneously in the abdominal area by the patient.

HAE is a rare, autosomal dominant disease caused by a deficiency or dysfunction of the C1 inhibitor, which is involved in regulating how certain immune system and blood clotting pathways function. The disease is characterized by recurrent episodes of nonpruritic, nonpitting, subcutaneous or 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. Typically, symptoms commence in childhood (often as early as 2 or 3 years of age), 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 3 days and others may 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 to 36 hours and then gradually subsides over the next 48 hours to 72 hours. The most common sites of swelling are the arms, legs, hands, feet, and abdomen. Attacks that impact the skin may cause patients to experience a sensation of uncomfortable stretching, tightness, or numbness. 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)

In August 2011, the FDA approved icatibant (Firazyr) Injection for the treatment of acute attacks of HAE in people ages 18 years and older. Firazyr is not approved for the prophylaxis of HAE attacks.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The efficacy and safety of Firazyr for the treatment of acute attacks of HAE in adults were studied in three controlled clinical trials. Among the 223 patients in these studies, the mean age was 38 years, 64% were female, and 95% were white. Approximately 57% of patients reported use of attenuated androgens, antifibrinolytic agents, or C1 inhibitors. Response to therapy was primarily assessed using visual analog scores on a 100 mm scale and patient- and physician-reported symptom scores for abdominal and cutaneous pain and swelling.

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Trial 1 was a randomized, placebo-controlled, double-blind, parallel-group study of 98 adult patients with a median age of 36 years. Patients who had developed moderate to severe cutaneous or abdominal or mild to moderate laryngeal attacks of HAE were randomized to receive either Firazyr 30 mg or placebo by subcutaneous injection. Patients with severe laryngeal attacks of HAE received open-label Firazyr 30 mg. The primary endpoint was assessed using a 3-item composite visual analog score (VAS), comprised of averaged assessments of skin swelling, skin pain, and abdominal pain. Response was defined as at least a 50% reduction from the pretreatment composite 3-item VAS score. The median time to 50% reduction in symptoms for patients with cutaneous or abdominal attacks treated with Firazyr (n = 43) compared to placebo (n = 45) was 2.0 hours [95% CI 1.5, 3.0] versus 19.8 hours [95% CI 6.1, 26.3], respectively ($p < 0.001$).

Other evaluated endpoints included time to almost complete symptom relief (VAS < 10 mm) and rescue medication use. In Trial 1, the median times to almost complete symptom relief were 8.0 versus 36.0 hours for Firazyr and placebo, respectively. In terms of rescue medication use, 3/43 (7%) patients treated with Firazyr used additional rescue medication in comparison to 18/45 (40%) patients treated with placebo.

In a second placebo-controlled trial and an active-controlled trial, a total of 26 and 35 patients, respectively, received Firazyr 30 mg for the treatment of an acute HAE attack. Across the three trials, Firazyr had a median time to 50% reduction from baseline symptoms ranging from 2.0 to 2.3 hours.

Recurrent attacks
In all three controlled trials, patients were eligible for treatment of subsequent attacks in an open-label extension. Patients were treated with Firazyr 30 mg and could receive up to 3 doses of Firazyr 30 mg administered at least 6 hours apart for each attack. A total of 225 patients were treated with 1,076 doses of 30 mg Firazyr for 987 attacks of acute HAE in these trials. In an assessment of the first 5 Firazyr -treated attacks (621 doses for 582 attacks), the median times to a 50% reduction from the pretreatment composite 3-item VAS score were similar across attacks (2.0, 2.0, 2.4, 2.0, 1.5 hours). The majority (93%) of these attacks of HAE were treated with a single dose of Firazyr.

Laryngeal attacks
A total of 60 patients with laryngeal attacks were treated with Firazyr in the controlled trials. Efficacy results were similar to those observed for non-laryngeal (cutaneous and abdominal) sites of attack.

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Self-administration
Self-administration of Firazyr by 56 patients was assessed in an open label trial. Patients who administered Firazyr during an acute attack of HAE had a median time to 50% reduction from the pretreatment composite 3-item VAS score of 2.6 hours.

Pediatric Patients
The safety and efficacy of a single subcutaneous dose of icatibant (0.4 mg/kg, max. 30 mg) in pediatric patients aged 2 years to younger than 18 years were evaluated in an open-label, nonrandomized, multicenter study in 32 patients with HAE. Efficacy was evaluated in 22 patients (11 children and 11 adolescents) who were treated during an attack, and safety was evaluated in these patients plus 10 adolescents who were treated without attack. The primary endpoint was time to onset of symptom relief. Overall, the median time to onset of symptom relief was 1 hour in the efficacy population. All treatment-emergent adverse events were classified as mild to moderate and included gastrointestinal symptoms and injection-site reactions which resolved by 6 hours post dose.

References

1. Firazyr (icatibant) [package insert]. Shire Orphan Therapies, Inc., Lexington, MA: August 2011.
2. Zuraw BL. Hereditary angioedema. N Engl J Med. 2008;359:1027-1036.
3. Cicardi M, Banerji A, Bracho F et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. N Engl J Med. 2010;363:532-541.
4. Bernstein JA. Hereditary angioedema: a current state-of-the-art review, VIII: current status of emerging therapies. Ann Allergy Asthma Immunol. 2008;100(suppl 2):S41-S46.
5. Farkas, Reshef, et al. Treatment Effect and Safety of Icatibant in Pediatric Patients with Hereditary Angioedema. J Allergy Clin Immunol Pract. 2017;6(6):1671-78.

Policy History

Original Effective Date: 03/21/2012
Current Effective Date: 11/11/2024
03/01/2012 Medical Policy Committee review
03/21/2012 Medical Policy Implementation Committee approval. New policy.
02/19/2013 Coding updated
03/07/2013 Medical Policy Committee review
03/20/2013 Medical Policy Implementation Committee approval. No change to coverage.

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03/06/2014	Medical Policy Committee review
03/19/2014	Medical Policy Implementation Committee approval. No change to coverage.
03/05/2015	Medical Policy Committee review
03/20/2015	Medical Policy Implementation Committee approval. No change to coverage.
03/03/2016	Medical Policy Committee review
03/16/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
03/02/2017	Medical Policy Committee review
03/15/2017	Medical Policy Implementation Committee approval. No change to coverage.
03/01/2018	Medical Policy Committee review
03/21/2018	Medical Policy Implementation Committee approval. No change to coverage.
03/07/2019	Medical Policy Committee review
03/20/2019	Medical Policy Implementation Committee approval. No change to coverage.
03/05/2020	Medical Policy Committee review
03/11/2020	Medical Policy Implementation Committee approval. No change to coverage.
09/14/2020	Coding update
12/03/2020	Medical Policy Committee review
12/09/2020	Medical Policy Implementation Committee approval. Title changed to reflect availability of generics. Generic added to policy with new criterion requiring trial of generic prior to brand. Also updated criteria to clarify that coverage is only eligible for treatment of acute attacks.
12/02/2021	Medical Policy Committee review
12/08/2021	Medical Policy Implementation Committee approval. No change to coverage.
07/07/2022	Medical Policy Committee review
07/13/2022	Medical Policy Implementation Committee approval. Removed age limitation from criteria and added relevant background information.
07/06/2023	Medical Policy Committee review
07/12/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/02/2024	Medical Policy Committee review
07/10/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

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10/03/2024 Medical Policy Committee review
10/08/2024 Medical Policy Implementation Committee approval. Updated criteria to add coverage for patients with type 3 HAE.
Next Scheduled Review Date: 10/2025

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 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.

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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	J1744
ICD-10 Diagnosis	All related diagnoses

*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:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (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 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.

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**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: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

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.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.