| Reference number(s) |
| --- |
| 2192-A |

# Standard Medicare Part B Management icatibant Products

## 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 |
| --- | --- |
| Firazyr | icatibant |
| Sajazir | icatibant |
| icatibant (all other brands) | icatibant |

## 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[1,2,15]

Treatment of acute attacks of hereditary angioedema (HAE) in adults 18 years of age and older.

### Compendial Uses[3]

Treatment of angiotensin-converting enzyme (ACE) inhibitor-induced angioedema.

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.


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# Documentation

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

## Hereditary Angioedema (HAE)

- 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, chart notes demonstrating a reduction in severity and/or duration of attacks

# Coverage Criteria

## Hereditary Angioedema (HAE)[1,2,4,6-15]

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:

- 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.


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### ACE Inhibitor-induced Angioedema[3,5,16]

Authorization of 3 days may be granted for acute management of ACE inhibitor-induced angioedema.

# Continuation of Therapy

### Hereditary Angioedema

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

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 a reduction in severity and/or duration of acute attacks.

### ACE Inhibitor-induced Angioedema

All members (including new members) requesting reauthorization for continuation of therapy must meet all requirements in the coverage criteria section.

# Summary of Evidence

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

- The prescribing information for Firazyr, Sajazir and generic icatibant.
- 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.


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- 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.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Firazyr, Sajazir, and generic icatibant are covered in addition to ACE inhibitor-induced angioedema.

# 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 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 Firazyr, Sajazir, and generic icatibant to treat ACE inhibitor-induced angioedema can be found in two published studies. Sinert and colleagues found that there was no significant difference in time to meeting discharge criteria between icatibant 30 mg injected subcutaneously and placebo in adults who presented within 12 hours of ACE inhibitor-induced angioedema of the head and/or neck of at least moderate severity (N=121). In both groups, the median time to meeting discharge criteria (defined as time from study drug administration to earliest absence of difficulty breathing or swallowing and mild or absent voice change and tongue swelling) was 4 hours. Median time to symptom resolution was 2 hours with icatibant and 1.6 hours with placebo, which was a nonsignificant difference. The median time to study drug administration after symptom onset was 7.8 hours, and more than 90% of patients also received


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corticosteroids, antihistamines, or epinephrine prior to the study drug. The most common ACE inhibitor taken by the patients was lisinopril (69.4%). Attack severity was moderate in 71.9% and severe or very severe in 28.1%. Black or African American patients made up 69.4% of the population. The most common treatment-related adverse events with icatibant were increased serum uric acid (n=2), increased neutrophil percentage (n=2), and dysphonia (n=2), and angioedema (n=3). Additionally, Bas and colleagues conducted a randomized trial (N=27) of adults who had ACE inhibitor-induced angioedema. All patients who received either icatibant 30 mg subcutaneously or the off-label standard therapy (prednisolone 500 mg IV plus clemastine 2 mg) achieved complete resolution of edema. However, the median time to complete resolution was significantly shorter with icatibant (8 vs 27.1 hours).

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