Icatibant (FIRAZYR®)
National Drug Monograph
June 2012

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM-MAP-VPE drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary

Icatibant injection (FIRAZYR), a bradykinin B2 receptor antagonist, is indicated for the treatment of acute attacks of hereditary angioedema (HAE) in patients ≥ 18 years of age.

Treatment with icatibant was evaluated in two published, randomized, double-blind, controlled trials (FAST-1, FAST-2) in patients presenting within 6 hours of acute cutaneous or abdominal symptoms of HAE of moderately severe intensity. In FAST-1, the primary endpoint (difference in median time to clinically significant relief of the index symptom) did not achieve statistical significance with icatibant 30 mg administered subcutaneously compared to placebo (2.5 hours vs. 4.6 hours, respectively; P=0.14). In FAST-2, there was a statistically significant improvement in the primary endpoint with icatibant compared to tranexamic acid (2.0 hours vs. 12.0 hours, respectively; P<0.001). In another published, randomized, double-blind, placebo-controlled trial of patients with HAE, the primary endpoint (difference in median time to clinically significant relief of the composite symptoms including cutaneous pain or swelling, or abdominal pain) was reduced with icatibant 30 mg subcutaneously compared to placebo (2.0 hours vs. 19.8 hours, respectively; P<0.001).

The product information for icatibant includes a warning that after patients are treated for laryngeal attacks with icatibant, they should seek immediate medical attention. Injection site reaction is the most frequently occurring adverse event and was reported in 97-100% of patients receiving icatibant in the clinical trials. Other frequently occurring adverse events with icatibant include pyrexia, increase in transaminases, dizziness and rash.

Icatibant should be administered as a dose of 30 mg (available as a single use pre-filled syringe of 30 mg/3 mL), as one subcutaneous injection of 3 mL into the skin of the abdomen. If the HAE attack continues despite the initial 30 mg dose of icatibant, additional doses may be administered (same instructions apply) at intervals of at least 6 hours, with no more than 3 injections in 24 hours.

Treatment with icatibant 30 mg significantly reduced the time to symptom relief compared to active control with tranexamic acid, with conflicting results compared to placebo in two trials of differing endpoints. Treatment with icatibant is reported to be well-tolerated, with a similar percentage of patients experiencing an adverse event as placebo; although, injection site reactions were reported in nearly all patients in the icatibant treatment groups.

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Introduction[1-6]

Icatibant injection (FIRAZYR, Shire) is a bradykinin B2 receptor antagonist, approved by the FDA August 25, 2011 for the treatment of acute attacks of hereditary angioedema (HAE) in patients ≥ 18 years of age.[1]

Hereditary angioedema is an autosomal dominant disorder caused by a deficiency in functional C1 inhibitor and has been estimated to affect approximately 1 in 50,000 persons (there are estimated to be approximately 6,000 patients in the United States with HAE). Typically, patients first present with symptoms in early childhood, with continued attacks for the duration of their lives. The frequency of attacks is variable, occurring on average every 1 to 2 weeks. Some patients will rarely experience an attack while others have them on a more frequent basis.[2]

The most common location for an acute attack is the skin or abdomen, with attacks of the skin most commonly involving the extremities, then face, genitals, and chest/neck. Symptoms may include swelling (most common in the hands, feet, arms, legs, and abdomen; less frequently involving the oropharynx) and a nonpruritic rash; often associated with tingling prior to the appearance of symptoms. Swelling may worsen over the first 24 hours then diminish over the next 2 to 3 days. Symptoms associated with the abdomen also include pain, nausea, vomiting, and hypotension due to a shift in fluid. Death has occurred with laryngeal angioedema. Triggers may include stress or trauma, including surgical or dental procedures; although, attacks may occur without a precipitating factor.[2]

Diagnosis can be made in a patient with a history of recurrent angioedema, and abdominal pain without urticaria. Measurement of C4 levels can be used to rule-out HAE, since nearly all patients with HAE will have decreased levels. Further testing may be conducted to evaluate the antigenic or functional C1 inhibitor level to determine the HAE type.[2,3] Patients with HAE have a mutation in the C1 inhibitor gene and may be classified as type I (85% of patients) or type II (15%), the two main types of HAE that result in reduced levels of antigenic (type I) and functional (type I and II) levels of C1 inhibitor. Another type of familial angioedema has been described, primarily involving women during pregnancy or who received estrogen therapy (although, this form has also been found in men), that present with normal levels of antigenic and functional C1 inhibitor.[2]

Management of HAE includes recognition and avoidance of potential triggers, treatment of acute symptoms, and short and long-term prophylaxis.[2-6] For the management of significant acute HAE attacks, use of C1 inhibitor, ecallantide, or icatibant are considered treatment options.[2-6] Fresh frozen plasma that contains C1 inhibitor has also been used for acute attacks although it is controversial as to whether treatment can exacerbate symptoms in some patients due to the potential for bradykinin production.[2,3,7] Symptom control of acute attacks includes narcotic analgesics for abdominal pain, antiemetics, and hydration. Intubation may be necessary in patients with oropharyngeal involvement if closure of the airway occurs.[2] The attenuated androgens (e.g., danazol, oxandrolone, stanozolol) and antifibrinolytics (e.g., aminocaproic acid, tranexamic acid) are more often used for long-term or short-term prophylaxis of HAE; although, they have been recommended in the management of acute HAE attacks, [2,5,6] despite not being adequately studied or to have confirmed benefit in this setting. The use of C1 INH has also been recommended in long-term prophylaxis.[2-6]

Pharmacology/Pharmacokinetics[1,2]

C1 inhibitor is found in human blood and is a serine protease inhibitor that is involved in the regulation of the complement and intrinsic coagulation or contact system pathway, as well as the fibrinolytic system. C1 inhibitor forms a complex with the protease causing inactivation. C1 inhibitor helps regulate activation of the contact system, by inactivation of coagulation factor XIIa and kallikrein, preventing the conversion of High Molecular Weight (HMW) kininogen to bradykinin, which is thought to be responsible for the symptoms associated with HAE and

increased vascular permeability. When there are low levels of functional C1 inhibitor, as in HAE, activation of the above pathways is not regulated.[2]

Icatibant is a competitive antagonist for the bradykinin B2 receptor and inhibits bradykinin from binding the B2 receptor, reducing the symptoms of acute HAE thought to be related to bradykinin (localized swelling, pain and inflammation).[1]

Pharmacokinetic Parameters	AUC (ng*hr/mL)	Cmax (ng/mL)	Tmax (hrs)	CL (mL/hr/kg)	Vd (L)	Half-life (hrs)
Icatibant 30 mg SC	2165±568	974±280	0.75	245±58	29.0±8.7	1.4±0.4

AUC=Area Under the Curve; CL=Plasma clearance; Cmax=maximum plasma concentration; SC=subcutaneously; Tmax=Time to Cmax; Vd=Volume of distribution

FDA Approved Indication[1]

Icatibant (FIRAZYR) is a bradykinin B2 receptor antagonist, approved for the treatment of acute attacks of HAE in patients ≥ 18 years of age.[1]

Potential Off-Label Uses[1,8-10]

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

Published clinical trial data are not available for the use of icatibant for on-demand therapy (product information[1]), or short-term prophylaxis (case report[8]) in patients with HAE. Icatibant has not been adequately studied (case series[9], case report[10]) for treatment of patients with angiotensin-converting enzyme inhibitor (ACEI)-induced angioedema and is therefore not recommended for this condition.

Current VA National Formulary Alternatives[2,5]

There are currently no VA National Formulary agents available that are indicated for the management of acute HAE.

An attenuated androgen (e.g., danazol) and antifibrinolytic (e.g., aminocaproic acid) are listed on the VA National Formulary and have been used in the management of acute HAE attacks, but due to the longer onset of action, are not typically recommended for treatment of acute attacks if other treatment options are available, especially if symptoms are severe or have laryngeal involvement.[2,5]

Dosage and Administration[1,6]

General Recommendations: Icatibant is available in a single-use, pre-filled syringe that delivers 3 mL containing 30 mg (10 mg/mL) of icatibant for subcutaneous injection. Icatibant should remain in the carton until ready for use and stored at a temperature of 36°F to 77°F (2°C to 25°C) and should not be frozen.[1] According to the manufacturer, the shelf-life of icatibant is up to 24 months. The solution should be colorless and clear and should not be used if any particulate material is visible or if the solution appears cloudy or is discolored. The contents of the syringe should be administered, over at least 30 seconds, into the skin of the abdominal area by subcutaneous injection. If the HAE attack continues despite the initial 30 mg dose icatibant, two additional doses, at intervals of at least 6 hours, may be administered (same instructions apply) within 24 hours.[1] It has been reported that 7 to 12% of patients will require a second dose, and a third dose in 1 to 3 % of patients.[6]

Recommended Dose for Treatment of Acute HAE Attacks

Availability	Dose
Icatibant 30 mg (10 mg/mL) single use pre-filled syringe	30 mg (3 mL) subcutaneously in the abdominal area, may repeat X 2 within 24 hours

Efficacy[11,12]

A literature search was performed on PubMed/Medline using the search terms icatibant and angioedema through 20 Jan 2012. The search was limited to clinical trials in humans that were published in the English language. Reference lists of review articles were searched for additional relevant clinical trials. All controlled trials published in peer-reviewed journals evaluating treatment with icatibant in patients with hereditary angioedema in other than healthy subjects were included. Two Phase III clinical trials (For Angioedema Subcutaneous Treatment or FAST) that evaluated icatibant in the treatment of patients presenting with an acute attack of HAE (FAST-1,[11] FAST-2[11]) were obtained using the above search method and met these criteria. One additional Phase III placebo-controlled clinical trial evaluating icatibant in patients with an acute attack of HAE (FAST-3[12]) was identified through a search of clinicaltrials.gov. Results of these three published controlled clinical trials are discussed below (details provided in the Appendix).

Efficacy Measures (Published Controlled Clinical Trials)[11,12]

Primary Endpoint

- Median time to clinically significant relief (decrease in visual-analogue scale [VAS] score of $\geq$ 20 to 30 mm for 3 consecutive measures) of index symptom (highest VAS for 1 of 3 symptoms: cutaneous swelling, cutaneous pain, abdominal pain; if combination of symptoms, abdominal pain selected as index symptom)[11]
- Time to 50% reduction symptom severity from baseline composite 3 symptoms (cutaneous swelling, cutaneous pain, abdominal pain) VAS score for 3 consecutive measures[12]

Secondary and Other Endpoints

- Median time to first improvement of index symptom[11]
- Median time to almost complete symptom relief (VAS score of 0 to 10 mm for 3 consecutive measures for all symptoms)[11]
- Percent of patients with clinically significant relief of index symptom at 4 hours[11]
- Median time to onset primary symptom relief[12]
- Median time to initial symptom improvement[12]
- Median time to almost complete symptom relief[12]
- Median time to onset symptom relief for individual symptoms per VAS[12]

Clinical Trial Data[11-13]

The efficacy and safety of icatibant 30 mg subcutaneously was evaluated in two phase III randomized, double-blind, controlled clinical trials (FAST-1 vs. placebo; FAST-2 vs. tranexamic acid) in patients with documented HAE (56 patients in FAST-1; 74 patients in FAST-2) who presented within 6 hours of an acute attack with cutaneous or abdominal symptoms becoming moderately severe in intensity. Patients were evaluated by rating the severity of three symptoms (cutaneous swelling, cutaneous pain, and abdominal pain) on VAS (0 mm=no symptoms; 100 mm=worst possible symptom severity), with an eligible attack being at least 30 mm for $\geq$ 1 of the three symptoms. The primary endpoint of the two trials was the median time to clinically significant relief (decrease in VAS score of $\geq$ 20 to 30 mm for three consecutive measures) of the index symptom (highest VAS score for one of the three specified symptoms).[11]

In FAST-1, the time to clinically significant relief was 2.5 hours with icatibant compared to 4.6 hours with placebo; a difference that did not achieve statistical significance (P=0.14). In FAST-2, the difference in the same primary endpoint was statistically significant, with relief reported at 2.0 hours with icatibant compared to 12.0 hours with tranexamic acid (P<0.001). The authors stated the reason for not achieving statistical significance in the primary endpoint in FAST-1 could have been attributed to using the change in only the index symptom as a marker for symptom relief, and the inclusion of data from patients who received rescue medication in the placebo group (i.e., 45% and 52% of patients on placebo received rescue medication within 12 and 48 hours, respectively; compared to 11% and 22%, respectively, of patients on icatibant). The difference in the secondary endpoint of time to first

improvement as assessed by patient and provider were significantly reduced with icatibant compared to placebo in FAST-1, and compared to tranexamic acid in FAST-2. Refer to Appendices for results of other secondary endpoints.[11]

FAST-3 evaluated icatibant 30 mg subcutaneously compared to placebo in patients presenting within 6 hours of acute symptoms of HAE (cutaneous and/or abdominal symptoms at least moderate in severity, or mild laryngeal symptoms). There were 10 patients in the laryngeal population; 5 randomized to icatibant or placebo, with 5 that received open-label icatibant (refer to Appendices for results of laryngeal population). The primary endpoint for the 88 patients in the nonlaryngeal population was median time to 50% reduction in symptom severity from baseline for a composite of three symptoms: cutaneous swelling, cutaneous pain, abdominal pain; with a VAS score of $\geq$ 30 mm for three consecutive measures. Treatment with icatibant significantly reduced the time to the primary endpoint compared to placebo (2.0 vs. 19.8 hours, respectively; P<0.001). The median time to initial onset of symptom relief (secondary endpoint) was also significantly reduced with icatibant compared to placebo, as assessed by both patient and provider. Refer to Appendices for results of other secondary endpoints.[12]

In addition, the manufacturer reports data from an open-label trial of 56 patients who self-administered icatibant during an acute HAE attack. Patients were eligible to self-administer after receiving their first dose by a healthcare professional and after being provided education on self-administration. The decision to treat was per the patient's self-assessed need for treatment. The median time to 50% reduction in composite symptom score (same primary endpoint as in FAST-3) was 2.6 hours (95% CI 2.0 to 4.0 hours). The median time to onset of administration of icatibant in the self-administration trial was reported as 4.5 hours; compared to 6.5 hours in FAST-3, 10.5 hours in FAST-2 and 7.6 hours in FAST-1. Injection site reactions were reported in 95% of patients in the self-administration study, with 8 reports of severe symptoms. Excluding injection site reactions, 32.1% of patients reported at least one adverse event, with the most common being HAE.[1,13]

Adverse Events (Safety Data)[1,11]

Deaths and Other Serious Adverse Events[1,11]

No deaths have been reported related to treatment with icatibant. According to clinical trial data, 5 patients experienced serious adverse events in the icatibant treatment group: gastroenteritis and hypertensive crisis; laryngeal attack of angioedema; abdominal attack of angioedema; cholelithiasis; laryngeal attack of angioedema requiring intubation. It was reported that none of these serious adverse events were attributed to treatment with icatibant.[11]

Common Adverse Events[1]

The most frequently occurring adverse event in patients receiving icatibant included injection site reactions (bruising, hematoma, burning, erythema, hypoesthesia, irritation, numbness, edema, pain, pressure sensation, pruritus, swelling, urticaria, and warmth). Pyrexia, increased transaminase levels, and dizziness also occurred more frequently compared to placebo. Other adverse reactions reported with icatibant included rash, nausea, and headache. For further details on the safety results as reported in the published clinical trials, refer to the Appendices.

Adverse Event[a] (> 1% and > placebo)	Icatibant (n=77) Number of Patients (%)	Placebo (n=75) Number of Patients (%)
Injection site reaction	75 (97)	25 (33)
Pyrexia	3 (4)	0
Increased transaminase	3 (4)	0
Dizziness	2 (3)	1 (1)

[a] Adverse events occurring within 14 days of study drug treatment in two placebo-controlled trials

Immunogenicity[1]

In clinical trials where patients received repeated treatment, 4 patients tested positive for anti-icatibant antibodies; with three of these patients having negative test results upon follow-up. There has been no association between anti-

icatibant antibodies and treatment efficacy. According to the manufacturer, there have been no reports of hypersensitivity or anaphylactic reactions in patients treated with icatibant.[1]

Sentinel Events

No data.

Contraindications[1]

There are no contraindications to icatibant listed in the manufacturer's product information.[1]

Warnings and Precautions[1]

Laryngeal Attacks: It is recommended that if the patient experiences an acute HAE attack with laryngeal involvement, that in addition to treatment with icatibant, they immediately seek medical attention at an appropriate healthcare facility due to the potential for airway obstruction.[1]

Specific Populations[1]

Pregnancy: Icatibant is Pregnancy Category C. Icatibant was found to result in delayed parturition, fetal death, and pre-implantation loss in rats and premature birth, abortion, fetal death, and pre-implantation loss in rabbits; although, no teratogenic effects were found. There are no well-controlled clinical trials of icatibant in pregnant females. Icatibant should only be used during pregnancy if the potential benefit outweighs the potential risk to the fetus.[1]
Labor and Delivery: The effects of icatibant have not been studied in this setting; however, icatibant has been shown to cause delayed parturition and fetal death in rats and premature birth and abortion in rabbits.[1]
Nursing Mothers: Icatibant is excreted in the milk of lactating rats. Caution should be used if icatibant is administered to a nursing mother as many drugs are excreted in human milk.[1]
Demographics (Age or Gender): The safety and effectiveness of icatibant has not been determined in patients under the age of 18 years. In a single-dose study, older patients had an approximate 2-fold increase in the AUC of icatibant compared to younger patients (e.g., 18 to 45 years of age); however, an adequate number of patients over the age of 65 have not been studied to establish if modifications to the recommendations for use of icatibant need to be made based on age. It was also noted that lower weight individuals and females have reduced clearance of icatibant, with an approximate 2-fold increase in AUC and Cmax compared to males. The manufacturer does not recommend dose adjustments based on age or gender since clinical experience has not identified a difference in safety or efficacy based on these demographics.[1]
Hepatic Impairment: No dose adjustment is recommended for icatibant in patients with hepatic impairment. The product information states there was no change noted in systemic exposure when icatibant was studied in patients with mild to moderate hepatic impairment (Child Pugh scores of 5 to 8).[1]
Renal Impairment: No dose adjustment is recommended for icatibant in patients with kidney impairment. According to the product information, icatibant has not specifically been studied in patients with kidney impairment; however, 10 of 37 patients treated with icatibant had hepatorenal syndrome with a glomerular filtration rate of < 60 ml/min. Icatibant is not expected to demonstrate a change in systemic exposure in patients with impaired kidney function since renal clearance is a minor elimination pathway.[1]

Nonclinical Toxicology[1]

Animal Toxicology and/or Pharmacology: There is the potential for icatibant to have a negative cardiovascular effect by interfering with the cardioprotective effects of bradykinin through antagonism of the B2 receptor. In animal studies involving the heart, icatibant decreased coronary blood flow and aggravated the duration of post-ischemic reperfusion arrhythmia; there was a doubling in the rate of mortality with intracoronary infusion of icatibant. There are limited data on the effect of icatibant in acute ischemia in humans. Icatibant should only be

used if the benefit exceeds the theoretical risk to patients during acute coronary ischemia, unstable angina pectoris, or in the weeks following a stroke.[1]

Look-alike/Sound-alike (LA/SA) Error Risk Potential

As part of a Joint Commission standard, LA/SA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LA/SA confusion:

NME Drug Name	Lexi-Comp	First DataBank	USP	ISMP	Clinical Judgment
Icatibant 30 mg/3 mL syringe for SC inj	None	None	None	None	Irbesartan Irinotecan
FIRAZYR	None	None	None	None	Famvir Fabrazyme

Drug Interactions[1]

No formal drug interaction studies have been conducted with icatibant. Metabolism of icatibant is not mediated by the CYP450 enzyme system.[1]

ACEIs: No pharmacokinetic or pharmacodynamics drug interaction action studies have been conducted with icatibant and an ACEI; however, due to their mechanism of action, there is the potential for icatibant to attenuate the antihypertensive effect of ACEIs.[1] Patients receiving an ACEI were excluded from the clinical trials with icatibant.[12,13]

Acquisition Costs

Refer to VA pricing sources for updated information.

Cost-Effectiveness Analysis

There are currently no published economic evaluations with icatibant.

Conclusions

Treatment with icatibant 30 mg administered subcutaneously significantly reduced the median time to symptom relief compared to active control with tranexamic acid (2.0 hours vs. 12.0 hours; P<0.001); although, the difference was not statistically significant when compared to placebo in one clinical trial (icatibant 2.5 hours vs. placebo 4.6 hours; P=0.14). The authors of the placebo-controlled trial concluded the lack of statistical significance may have been due, in part, to the inclusion of data from patients in the placebo group who received early rescue treatment, and that relief was determined based on an index symptom. In a follow-up placebo-controlled trial that evaluated relief based on a composite of symptoms, treatment with icatibant significantly reduced the median time to onset of symptom relief compared to placebo (2.0 hours vs. 19.8 hours, respectively; P<0.001).

Treatment with icatibant is reported to be well-tolerated, with a similar percentage of patients experiencing an adverse event as placebo, except for injection site reactions that were reported in the majority of patients in the icatibant treatment groups.

In patients with HAE, treatment with icatibant has not been compared to other recently approved therapies used for acute HAE attacks (e.g., C1 esterase inhibitor, ecallantide). C1 inhibitor and ecallantide have also been found to be effective in the treatment of acute HAE attacks (i.e., by reducing the time to onset of relief compared to placebo, or

demonstrating a greater improvement from baseline in patient-reported outcome measures compared to placebo, respectively); however, direct comparison trials to each other or with icatibant are not available. In addition, different inclusion criteria and measurement of efficacy parameters have been used in these clinical trials.

Published clinical trial results of icatibant for on-demand therapy in HAE, or in angioedema other than HAE are currently not available.

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Appendix: Published Controlled Clinical Trials with Icatibant in Acute HAE (FAST-1)

Citation	Eligibility Criteria	Interventions/Endpoints	Efficacy Results	Safety/Study Analysis
FAST-1 Cicardi M et al, 2010[11] R, DB, MC, PC U.S., Canada, Australia, Argentina n=56 (ITT) Supported by Jerini; NIH	**Inclusion** ≥ 18 yrs of age, documented type I or II HAE, no later than 6 hrs of an acute attack becoming at least moderately severe **Exclusion** Pregnant or lactating, angioedema other than HAE, serious concomitant illness, receipt of pain medication for the acute attack, C1 INH within 3 days, tranexamic acid within 7 days, on an ACEI	**Treatment** Icatibant 30 mg SC or Placebo OL icatibant given if second attack requiring tx, or if potentially life-threatening laryngeal angioedema; rescue tx (C1 INH, antiemetics, opiates) allowed but withheld as long as possible (preferably 8 to 9 hrs) Pt assessed sx by VAS every 30 min between 1 to 4 hrs after tx, then at 5, 6, 8, 10, and 12 to 15 hrs; then 3 times/d from day 2 to 5 or until sx decreased **Endpoints** Primary: Median time to clinically sig relief (decrease in VAS score of ≥ 20 to 30 mm for 3 consecutive measures) of index sx (highest VAS for 1 of 3 sx: cutaneous swelling, cutaneous pain, abdominal pain; if combination, abdominal pain selected as index sx) Secondary: median time to 1st improvement of index sx; median time to almost complete sx relief (VAS score of 0 to 10 mm for 3 consecutive measures for all sx); % pts with clinically sig relief of index sx at 4 hrs R by study center and site of edema. Cutaneous or abdominal attacks; rate severity of 3 specific sx (cutaneous swelling, cutaneous pain, and abdominal pain) on VAS (0 mm=no sx; 100 mm=worst possible sx severity); eligible attack=at least 30 mm for ≥ 1 of the 3 sx	**Baseline** Mean age: 35 yrs; Male gender: 41% icatibant, 28% placebo; Attack type: cutaneous (14 icatibant, 13 placebo), abdominal (13 icatibant, 16 placebo) **Results** See table below **Rescue medication** Within 12 hrs: Icatibant 3 pts (11%); Placebo 13 pts (45%) Within 48 hrs: Icatibant 6 pts (22%); Placebo 15 pts (52%) **Laryngeal attacks (n=8; OL icatibant)** Median time to 1st improvement (per pt): 0.6 hrs No sx at 4 hrs (per provider): 7 pts (87.5%) 3 pts with laryngeal attacks received rescue medication **Study Conclusions** Nonsignificant difference in primary endpoint of time to clinically significant relief of index sx in patients tx with icatibant compared to placebo	**Withdrawals** No deaths or withdrawals due to AEs in either group Study discontinuation: Icatibant 3 pts (1 withdrew consent, 2 other reasons); Placebo 2 pts (1 lost to f/u, 1 other reasons) **Adverse Events** See table below Recurrent or worsening HAE attack: Icatibant 4 (14.8%); Placebo 5 (17.2%) **Study Analysis** • Stringent definition of end point (change in only index sx) and analysis (inclusion of pts with rescue tx in placebo group) listed by authors as potential reasons for lack of statistical sig in primary endpoint vs. placebo • Statistically sig difference in primary endpoint with icatibant vs. placebo in post hoc analysis when data censored for pts receiving rescue tx • Patient specific rescue tx used not shown • Endpoint selected to determine clinically significant sx improvement and to account for potential incomplete blinding due to injection site reactions with icatibant • Authors state that trial may have been underpowered to detect a clinically meaningful difference between tx groups (i.e., it was powered to detect a difference of 5.5 hrs whereas actual difference was 2.1 hrs, which may be clinically meaningful) • Most common AE recurrent/worsening HAE attack; authors note may indicate requirement of another dose or agent for complete sx control in clinical practice

	Icatibant (n=27)	Placebo (n=29)	P value
Time to clinically sig relief of index sx[a]			
Median (hrs)	2.5	4.6	0.14
IQR	1.1 to 6.0	1.8 to 10.2	
Time to 1st sx improvement (per pt)			
Median (hrs)	0.8	16.9	<0.001
IQR	0.5 to 2.0	3.2 to NA	
Time to 1st sx improvement (per provider)			
Median (hrs)	1.0	5.7	<0.001
IQR	0.08 to 2.0	2.0 to 11.2	
Time to almost complete sx relief			
Median (hrs)	8.5	19.4	0.08
IQR	2.5 to 31.5	10.2 to 55.7	
Clinically sig relief of index sx at 4 hrs			
% Pts (95% CI)	67 (46 to 84)	46 (28 to 66)	0.18

[a] Primary endpoint

AE	Icatibant	Placebo
Any	12 (44%)	19 (66%)
Drug related AE	4 (15%)	1 (3%)
SAE	0	0
Injection site rxn[a]	26 (96%)	8 (28%)

[a] Injection site rxns were recorded separately from other AEs

ACEI=angiotensin-converting enzyme inhibitor; AE=adverse event; C1 INH=C1 inhibitor; CI=confidence interval; d=day; DB=double-blind; f/u=follow-up; HAE=hereditary angioedema; hrs=hours; IQR-interquartile range; ITT=intent-to-treat; MC=multicenter; min=minutes; n=number of patients; NA=not available; OL=open-label; PC=placebo-controlled; pt=patient; R=randomized; rxn=reaction; SAE=serious adverse event; SC=subcutaneous; sig=significant; sx=symptom; tx=treatment; VAS=visual-analogue scale; yrs=years

Appendix: Published Controlled Clinical Trials with Icatibant in Acute HAE (FAST-2)

Citation	Eligibility Criteria	Interventions/Endpoints	Efficacy Results	Safety/Study Analysis
FAST-2 Cicardi M et al, 2010[11] R, DB, MC, AC Germany, France, U.K., Israel, Hungary, Italy, Lithuania, Poland, Sweden, Switzerland, Austria, Ireland n=74 (ITT) Supported by Jerini	**Inclusion** ≥ 18 yrs of age; documented type I or II HAE; no later than 6 hrs of an acute attack becoming at least moderately severe **Exclusion** Pregnant or lactating, angioedema other than HAE, serious concomitant illness, receipt of pain medication for the acute attack, C1 INH within 3 days, tranexamic acid within 7 days, or on an ACEI	**Treatment** Icatibant 30 mg SC or Tranexamic acid 3 gm daily X 2 days OL icatibant given if second attack requiring tx, or if potentially life-threatening laryngeal angioedema; rescue tx (C1 INH, antiemetics, opiates) allowed but withheld as long as possible (preferably 8 to 9 hrs) **Endpoints** Primary: Median time to clinically sig relief (decrease in VAS score of ≥ 20 to 30 mm for 3 consecutive measures) of index sx (highest VAS for 1 of 3 sx: cutaneous swelling, cutaneous pain, abdominal pain; if combination, abdominal pain selected as index sx) Secondary: median time to 1st improvement of index sx; median time to almost complete sx relief (VAS score of 0 to 10 mm for 3 consecutive measures for all sx); % pts with clinically sig relief of index sx at 4 hrs R by study center and site of edema. Cutaneous or abdominal attacks; rate severity of 3 specific sx (cutaneous swelling, cutaneous pain, and abdominal pain) on VAS (0 mm=no sx; 100 mm=worst possible sx severity); eligible attack=at least 30 mm for ≥ 1 of the 3 sx	**Baseline** Mean age: 41 yrs; Male gender: 33% icatibant, 39% tranexamic acid; Attack type: cutaneous (24 icatibant, 23 tranexamic acid), abdominal (12 icatibant, 15 tranexamic acid) **Results** [a] Primary endpoint **Rescue medication** Within 12 hrs: Icatibant 0 pts; Tranexamic acid 5 pts (13%) Within 48 hrs: Icatibant 6 pts (17%); Tranexamic acid 11 pts (29%) **Laryngeal attacks (n=3; OL icatibant)** Median time to 1st improvement (per pt): 1.0 hr No sx at 4 hrs (per provider): 2 pts (66.7%) None of the 3 pts with laryngeal attacks received rescue medication **Study Conclusions** Statistically significant decrease in primary endpoint of time to clinically significant relief of index sx in patients tx with icatibant compared to tranexamic acid	**Withdrawals** 1 death (sudden cardiac death) in the tranexamic acid tx group No withdrawals due to AEs in either group Study discontinuation: Icatibant 10 pts (2 withdrew consent, 4 lost to f/u, 3 other reasons, 1 sig medical condition); Tranexamic acid 10 pts (1 withdrew consent, 2 lost to f/u, 5 other reasons, 1 sig medical condition, 1 severe aortic valve sclerosis and sudden cardiac death) **Adverse Events** [a] Injection site rxns were recorded separately from other AEs Recurrent or worsening HAE attack: Icatibant 10 (27.8%); Placebo 6 (15.8%) **Study Analysis** • Endpoint selected to determine clinically significant sx improvement and to account for potential incomplete blinding due to injection site reactions with icatibant • Rescue therapy more common in tranexamic acid tx group (although not as frequent as in placebo group of FAST-1) • Choice of comparator not typically recommended for acute HAE; comparison to other tx approved for acute HAE (C1 INH or ecallantide) would have been useful • Most common AE recurrent/worsening HAE attack; authors note may indicate requirement of another dose or agent for complete sx control in clinical practice

	Icatibant (n=36)	Tranexamic acid (n=38)	P value
Time to clinically sig relief of index sx[a]			
Median (hrs)	2.0	12.0	<0.001
IQR	1.0 to 3.5	3.5 to 25.4	
Time to 1st sx improvement (per pt)			
Median (hrs)	0.8	7.9	<0.001
IQR	0.4 to 1.4	1.1 to NA	
Time to 1st sx improvement (per provider)			
Median (hrs)	1.5	6.9	<0.001
IQR	0.7 to 3.0	4.0 to 13.8	
Time to almost complete sx relief			
Median (hrs)	10.0	51.0	<0.001
IQR	2.8 to 23.2	12.0 to 79.5	
Clinically sig relief of index sx at 4 hrs			
% Pts (95% CI)	80 (63 to 92)	31 (16 to 48)	<0.001

AE	Icatibant	Tranexamic Acid
Any	19 (53%)	16 (42%)
Drug related AE	5 (14%)	4 (11%)
SAE	4 (11%)	1 (3%)
Injection site rxn[a]	35 (97%)	10 (26%)

AC=active-controlled; ACEI=angiotensin-converting enzyme inhibitor; AE=adverse event; C1 INH=C1 inhibitor; CI=confidence interval; DB=double-blind; f/u=follow-up; HAE=hereditary angioedema; hrs=hours; IQR-interquartile range; ITT=intent-to-treat; MC=multicenter; n=number of patients; NA=not available; OL=open-label; pt=patient; R=randomized; SAE=serious adverse event; SC=subcutaneous; sig=significant; sx=symptom; tx=treatment; VAS=visual-analogue scale; yrs=years

Appendix: Published Controlled Clinical Trials with Icatibant in Acute HAE (FAST-3)

Citation	Eligibility Criteria	Interventions/Endpoints	Efficacy Results	Safety/Study Analysis
FAST-3 Lumry WR et al, 2011[12] R, DB, MC, PC U.S., Israel, Australia, Romania, Russia, Hungary, South Africa, Canada, Ukraine n=88 (nonlaryngeal ITT) Funded by Jerini AG/Shire Human Genetic Therapeutics	**Inclusion** ≥ 18 yrs of age; documented type I or II HAE or predefined medical history; no later than 6 hrs of an acute attack becoming at least moderate (abdominal and/or cutaneous) or mild (laryngeal) in severity, and within 12 hrs of attack onset **Exclusion** Pregnant or breast-feeding, angioedema other than HAE, previous icatibant tx, in other clinical trial within past 30 days, serious concomitant illness, receipt of pain medication for the acute attack, tx with an ACEI	**Treatment** Icatibant 30 mg SC or Placebo OL icatibant given if second attack requiring tx, or if severe laryngeal sx; rescue tx (C1 INH, antiemetics, opiates, NSAIDs, FFP, epinephrine) allowed Pt assessed sx by VAS every 30 min between 1 to 4 hrs after tx, then at 5, 6, 8, and 12 hrs **Endpoints** (nonlaryngeal) Primary: Time to 50% reduction sx severity from baseline composite 3 sx (skin swelling, skin pain, abdominal pain) VAS score of ≥ 30 mm for 3 consecutive measures Secondary: median time to onset primary sx relief; median time to initial sx improvement; median time to almost complete sx relief; median time to onset sx relief for individual sx per VAS R by site of edema (nonlaryngeal; mild to moderate laryngeal sx) Cutaneous or abdominal attacks rated by VAS (0 mm=no sx; 100 mm=worst possible sx severity) for severity of 3 specific sx (cutaneous swelling, cutaneous pain, and abdominal pain) with eligible attack=at least 30 mm for ≥ 1 of the 3 sx Laryngeal attack by VAS-5 point scale (0=no sx; 4=very severe sx)	**Baseline** (nonlaryngeal) Mean age: 36 yrs; Male gender: 36%; Race: 89% White **Results** [a] Primary endpoint [b] Placebo values for time to onset sx relief (per provider) not evaluable since < 50% pts attained sx relief At 4 hrs, 74% of pts felt their cutaneous or abdominal sx had much- or very-much improved vs. 24% in the placebo group (P<0.001) **Rescue medication** Before sx relief (primary endpoint): Icatibant 0 pts; Placebo 16 pts (36%) At any time up to 5 days: Icatibant 3 pts (7%); Placebo 18 pts (40%) **Laryngeal attacks** (n=10; Icatibant 3 pts, Placebo 2 pts, OL Icatibant 5 pts) Time to onset sx relief (50% decrease in VAS-5): Icatibant 2.5 hrs; Placebo 3.2 hrs (1 pt received OL Icatibant due to severe sx; 1 rescue tx w/Icatibant at 3.4 hrs); OL Icatibant 2.3 hrs **Study Conclusions** Statistically significant difference in primary endpoint of time to onset sx relief of composite sx in patients tx with icatibant compared to placebo	**Withdrawals** No deaths or withdrawals due to AEs in icatibant tx group; 1 death occurred in placebo group **Adverse Events** Recurrent or worsening HAE attack: Icatibant 5 (10.9%); Placebo 10 (21.7%) **Study Analysis** • Definition of primary endpoint changed from FAST-1 to include change in composite sx rather than index sx • Patient specific rescue tx used not shown • Primary endpoint evaluated by VAS score through 12 hrs; median time to endpoint 19.8 hrs in placebo group (95% CI 6.1 to 26.3 hrs); pts who did not achieve sx relief within observation period were censored at last observation time (Icatibant 0; Placebo 3)

	Icatibant (n=43)	Placebo (n=45)	P value
Time to onset sx relief (i.e., 50% reduction sx severity)[a]			
Median (hrs)	2.0	19.8	<0.001
95% CI	1.5 to 3.0	6.1 to 26.3	
Time to onset primary sx relief			
Median (hrs)	1.5	18.5	<0.001
95% CI	1.0 to 2.0	3.6 to 23.9	
Time to initial sx relief(per pt)			
Median (hrs)	0.8	3.5	<0.001
95% CI	0.5 to 1.0	1.9 to 5.4	
Time to initial sx relief (per provider)			
Median (hrs)	0.8	3.4	<0.001
95% CI	0.6 to 1.3	2.6 to 6.0	
Time to almost complete sx relief			
Median (hrs)	8.0	36.0	0.12
95% CI	5.0 to 42.5	29.0 to 50.9	
Time to onset sx relief (per pt)[b]			
Median (hrs)	2.0	8.0	<0.001
95% CI	1.5 to 2.0	4.0 to 23.9	

AE	Icatibant n=46	Placebo n=46
≥ 1 AE	19 (41.3%)	24 (52.2%)
Drug related AE	5 (10.9%)	3 (6.5%)
SAE	0	3 (6.5)
Injection site rxn	100%	41%

ACEI=angiotensin-converting enzyme inhibitor; AE=adverse event; C1 INH=C1 inhibitor; CI=confidence interval; DB=double-blind; FFP=fresh frozen plasma; f/u=follow-up; HAE=hereditary angioedema; hrs=hours; ITT=intent-to-treat; MC=multicenter; min=minutes; n=number of patients; NSAIDs=non-steroidal anti-inflammatory drugs; OL=open-label; PC=placebo-controlled; pt=patient; R=randomized; rxn=reaction; SAE=serious adverse event; SC=subcutaneous; sig=significant; sx=symptom; tx=treatment; VAS=visual-analogue scale; yrs=years

Appendix: Product Comparison (refer to individual VA National Drug Monographs www.pbm.va.gov)

	Icatibant (FIRAZYR)	Ecallantide (KALBITOR)	C1 Inhibitor (BERINERT)	C1 Inhibitor (CINRYZE)
FDA indication	Acute attacks HAE	Acute attacks HAE	Acute abdominal, facial or laryngeal attacks of HAE	Routine prophylaxis against HAE attacks
Published clinical trial data in HAE	Acute HAE	Acute HAE	Acute HAE[a]	Prophylaxis HAE Acute HAE On-demand therapy HAE
HAE attack location studied	Abdominal, cutaneous HAE; laryngeal HAE (OL tx)	HAE attack of any location	Abdominal, facial HAE; open-label extension: abdominal, facial, peripheral or laryngeal HAE	HAE attack of any location
Inclusion RCT (Acute HAE)	Report w/in 6 hours acute HAE becoming moderately-severe (Study 1 &2: abdominal, cutaneous; Study 3: abdominal, cutaneous; laryngeal OL tx)	Report w/in 8 hours acute HAE becoming moderate-severe	Report w/in 5 hours acute facial or abdominal HAE becoming moderate in intensity	Report w/in 4 hours acute HAE; moderate-severe abdominal, facial, genital (most severe=defining site); laryngeal OL tx
Primary Endpoint	(Study 1& 2) Median time to clinically significant relief (1st of 3 measures ≥ 20 to 30 mm reduction in VAS of 0 to 100 mm) of index sx (Study 3) Median time to onset relief (50% reduction sx severity) composite sx	(Study 1) Tx outcome score (+100 significant improvement to -100 significant worsening) at 4 hrs (Study 2) Change sx score (0 normal to 3 severe) at 4 hrs	Median time to onset relief (1st of 3 reports of relief or resolution at defining site) assessed per questions at intervals for up to 24 hrs	Acute: Median time to onset relief (1st of 3 reports of improvement at defining site) assessment per standard questionnaire every 15 min up to 4 hrs Prophylaxis: Number attacks per 12 wk tx period
Treatment Comparison	(Study 1 & 3) Icatibant 30 mg SC vs. placebo (Study 2) Icatibant 30 mg SC vs. tranexamic acid 3 gm daily X 2 days	Ecallantide 30 mg SC vs. placebo	C1 INH 10 or 20 units/kg IV vs. placebo	Acute: C1 INH 1000 units IV vs. placebo Prophylaxis: C1 INH 1000 units IV 2 x/wk vs. placebo
Results	PEP (Study 1): 2.5 hrs vs. 4.6 hrs (P=0.14) Median time to almost complete sx relief: 8.5 hrs vs. 19.4 hrs (P=0.08) PEP (Study 2): 2.0 hrs vs. 12.0 hrs (P<0.001) Median time to almost complete sx relief: 10.0 hrs vs. 51.0 hrs (P<0.001) PEP (Study 3): 2.0 hrs vs. 19.8 hrs (P<0.001) Median time to almost complete sx relief: 8.0 hrs vs. 36.0 hrs (P<0.001)	PEP (Study 1): Median 50 vs. 0 (P=0.004) Median time to onset overall sx improvement: 2.75 hrs vs. > 4 hrs (P=0.14) PEP (Study 2): Median -1 vs. 0 (P=0.01)	PEP: 0.5 hrs (20 units/kg) vs. 1.5 hrs (P=0.0025) Median time to complete resolution: 4.92 hrs vs. 7.79 hrs (P=0.0237)	PEP (Acute): 2 hrs vs. > 4 hrs (P=0.02) Median time to complete resolution: 12.3 hrs vs. 25 hrs (P=0.004) Prophylaxis: 6.26 vs. 12.73 attacks (P<0.001)
Product Description	Synthetic decapeptide with 5 non-proteinogenic amino acids	Amino acid protein produced in *Pichia pastoris* yeast cells by recombinant DNA technology	Derived from human plasma (pasteurized)	Derived from human plasma (pasteurized, nanofiltered)
Warnings and Precautions	Seek immediate medical attention if acute laryngeal HAE attack	Boxed warning for anaphylaxis	Hypersensitivity Risk for transmission of infectious agents Thrombotic events	Hypersensitivity Risk for transmission of infectious agents Thrombotic events

Comparison continued	Icatibant (FIRAZYR)	Ecallantide (KALBITOR)	C1 Inhibitor (BERINERT)	C1 Inhibitor (CINRYZE)
Product availability	One ready-to-use pre-filled syringe of 30 mg/3 mL required to deliver 30 mg administered SC	Package containing 3 single-use vials each with 10 mg/mL (1 mL), with 3 separate SC injections required to administer dose of 30 mg	Kit containing 500 units powder in single-use vial for reconstitution with 10 mL sterile water and Mix2Vial transfer set; required number of vials are reconstituted to obtain dose of 20 units per kg combined in syringe, with use of IV administration set to deliver dose at rate of 4 mL/min	Available as 500 units powder for reconstitution with 5 mL sterile water using double-ended transfer needle for concentration 100 units/mL; combining 2 vials in syringe, with use of appropriate needle/IV administration set for delivery of 1000 units dose at rate of 1 mL/min over 10 min
Dose	30 mg	30 mg	20 units per kg	1000 units
Route of administration	SC injection (one 3 mL injection) Instructions and training available for self-administration	SC injection (3 injections per dose) Recommendations to only be administered by healthcare professional with medical support available to manage anaphylaxis and HAE	IV infusion (4 mL/min) (duration of infusion depends on dose based on weight) Approved for on-demand self- administration; instructions and training available	IV infusion (1mL/min) (10 min per dose) Instructions and training available for self-administration
Storage	36° to 77° F Store in container until ready to use	Refrigerate (36° to 46° F) Protect from light	36° to 77° F Protect from light	36° to 77° F Protect from light
Shelf-life	Up to 24 months	Up to 36 months	Up to 30 months	Up to 24 months

[a] U.S. product only studied in acute HAE; HAE prophylaxis and on-demand therapy studied with product available outside U.S.
C1 INH=C1 inhibitor; HAE=hereditary angioedema; hrs=hours; IV=intravenous; min=minute; OL=open-label; SC=subcutaneous; sx=symptom; tx=treatment; VAS=visual-analogue scale