

Icatibant (FIRAZYR®): Angiotensin-Converting Enzyme Inhibitor Induced Angioedema National Drug Monograph Addendum June 2015

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

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made 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 Documents will be placed in the Archive section when the information is deemed to be no longer current.

This addendum to the original drug monograph provides information on the evidence for the use of icatibant in patients presenting with angiotensin-converting enzyme inhibitor-induced angioedema (off-label). The original drug monograph can be found at: [PBM MAP VPE National Drug Monographs](#)

Introduction

Icatibant injection (FIRAZYR) 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 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

The incidence of angioedema in patients taking an angiotensin-converting enzyme inhibitor (ACEI) is approximately 0.1-1.2%. The exact mechanism of ACEI-induced angioedema is unknown; although, it is thought to be related to an accumulation of bradykinin. In an evaluation of veteran patients initiating treatment with an ACEI, 0.2% reported to have experienced angioedema, with rates being four times higher in black patients and 50% higher in women.²

Although most reports of ACEI-induced angioedema are mild, and do not result in airway obstruction, they can be life-threatening if there is oropharyngeal-laryngeal involvement.³ When patients with ACEI-induced angioedema present with impending airway obstruction, standard pharmacologic treatment may include antihistamines, corticosteroids, with or without epinephrine; however, with the mechanism thought to be primarily related to increased bradykinin rather than histamine, the efficacy of this practice has been questioned for ACEI-induced angioedema.³ Fresh frozen plasma, which contains angiotensin-converting enzyme, has also been used and found to be beneficial;⁴ however, there is also concern for potential transfusion of complement factor, which could exacerbate symptoms in some patients with HAE.⁴

Several of the agents indicated for the management of HAE have also been used in patients with ACEI-induced angioedema. Although no clinical trials are available at this time, case reports are available that demonstrate the potential benefit of using a C1 esterase inhibitor in the management of patients presenting for emergency treatment of ACEI-induced angioedema.⁵⁻⁷ There are also two published phase 2 clinical trials evaluating the use of ecallantide compared to conventional therapy that did not find a statistically significant difference in the percent improvement in patients receiving ecallantide.^{8,9} The authors stated that additional data are needed to confirm the potential benefit⁸ or to evaluate benefit in patients presenting with more severe symptoms of ACEI-induced angioedema.⁹ With the mechanism of action of icatibant, and case reports of potential benefit,¹⁰⁻¹³ it has been hypothesized that this agent may be useful for the management of ACEI-induced angioedema.

In January 2015, results of a clinical trial comparing icatibant to standard therapy for emergency management of ACEI-induced angioedema were published,¹⁴ and are presented below.

Efficacy (Off-Label Use for ACEI-Induced Angioedema)

Review of Efficacy¹⁴

- The results of icatibant in the management of patients with ACEI-induced angioedema are available from one published multicenter, randomized, double-blind, double-dummy, phase 2 study that evaluated the median time to complete resolution of edema. Patients receiving treatment with an ACEI who presented to the emergency

room with ACEI-induced angioedema of the upper aerodigestive tract (i.e., the face, lips, cheeks, tongue, soft palate or uvula, pharynx, larynx), and were within 10 hours of onset of the attack, were randomized to subcutaneous (SC) icatibant 30 mg or standard therapy with intravenous (IV) prednisolone 500mg and clemastine 2 mg. Placebo (normal saline) was also administered IV to patients randomized to icatibant, and SC to patients receiving standard therapy.

- The following patients were excluded from the trial: angioedema prior to initiation of an ACEI; angioedema thought to be due to a cause other than an ACEI; acute urticaria; unstable angina; acute myocardial infarction; acute heart failure with New York Heart Association (NYHA) class III or IV; pregnancy; lactation.
- Efficacy was evaluated by:
 - the patient using a visual analogue scale (VAS) (range 0 to 10; with 10 indicating more severe symptoms) for six symptoms: pain, shortness of breath, dysphagia, change in voice, sensation of a foreign body, and feeling of pressure at baseline, and 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours after treatment. An average of the six symptoms was calculated for a composite score.
 - the investigators evaluated response by VAS from 0 (no symptoms) to 3 (severe symptoms) for the six symptoms, with calculation of a composite score.
 - a composite angioedema score was also calculated based on the average of the scores as assessed by the investigator for four locations (lips and cheeks, tongue, oropharynx, hypopharynx or larynx) on a scale of 0 (no angioedema) to 4 (very severe angioedema).
- The primary endpoint of time to complete resolution of edema was assessed by the investigator and patient-assessed symptom scores, and investigator physical examination of the severity of angioedema. Secondary endpoints included: patients who did not respond to treatment defined as requiring rescue therapy (allowed after 6 hours if no reduction in symptoms; or if life-threatening symptoms, intervention including intubation or tracheotomy could be instituted); patients with complete resolution at 4 hours after treatment; time to onset of symptom relief (first improvement of at least one point in the composite score per investigator assessment, the angioedema score, or the patient assessment per VAS); and change in composite score from baseline to each evaluation time-point.
- A total of 30 patients (15 in each group) were enrolled in the trial; 3 patients were excluded due to receiving treatment per the investigator prior to randomization. Baseline characteristics of the 27 patients were as follows: 100% Caucasian; 63% male; 37% previous ACEI-induced angioedema. The mean age of study participants was 62.4 years for those on icatibant and 69.4 years for patients who received standard therapy. The most frequent location of angioedema symptoms included the tongue (67%) and floor of mouth (56%). Median time to onset of angioedema to treatment in patients randomized to icatibant was 6.1 hours (range 3 to 10 hours), and 5.1 hours (range 2 to 9.3 hours) in patients treated with standard therapy. Baseline scores for the severity of symptoms are included in the table below.

Baseline Symptom Scores

Baseline Assessment	Icatibant (N=13)	Standard Therapy (N=14)
	(+ Standard Deviation)	
Composite investigator symptom score ^a	1.1 (0.2)	1.2 (0.2)
Composite investigator angioedema score ^b	1.1 (0.2)	1.1 (0.2)
Composite patient VAS score ^c	2.9 (0.6)	3.5 (0.6)

VAS=Visual Analogue Scale

^a Scale of 0 (no symptoms) to 3 (severe symptoms)

^b Scale of 0 (no angioedema) to 4 (very severe angioedema)

^c Scale of 0 to 10, with higher scores indicating more severe symptoms

- All patients had complete resolution of symptoms. Three patients in the standard therapy treatment group required rescue therapy (one of which required a tracheotomy), and were considered treatment failures. These patients were censored at the time of rescue therapy and were assigned the maximum recorded time to complete resolution of edema (i.e., 61.2 hours; which occurred in the icatibant treatment group). According to sensitivity analysis, the primary efficacy endpoint in the icatibant and standard therapy treatment groups, respectively, was 8.0 vs. 21.2 hours when evaluating the actual time to complete resolution, and 8.0 vs. 23.7 hours when censoring the three patients who received rescue therapy. The primary endpoint of median time to complete resolution of symptoms was significantly reduced with icatibant compared to standard therapy (refer to Table below).

Study Results

Endpoint	Icatibant (N=13)	Standard Therapy (N=14)	P
Time (hrs) to complete resolution of edema; ^a median (IQR)	8.0 (3.0 to 16.0)	27.1 (20.3 to 48.0)	0.002
Complete resolution of edema at 4 hrs; n (%)	5 (38)	0	0.02
Time (hrs) to onset symptom relief; ^b median (95% CI)			
Per composite investigator symptom score	2.0 (1.0 to 8.1)	11.7 (8.0 to 18.0)	0.03
Per composite investigator angioedema score	2.0 (2.0 to 6.3)	7.9 (1.2 to 11.8)	0.36
Per composite patient VAS score	2.0 (2.0 to 12.0)	12.0 (11.3 to NE)	0.003

CI=confidence interval; hrs=hours; IQR=interquartile range; NE=not estimable

^a Primary endpoint

^b Time to first improvement of ≥ 1 point in composite score

- The trial was supported by an educational grant from Shire and by a grant from the Federal Ministry of Education and Research of Germany.
- Overall, there is moderate quality of evidence for the use of icatibant for the reduction in time to response of an acute ACEI-induced angioedema attack compared to standard therapy with a corticosteroid and antihistamine (Refer to Appendix A).

Safety¹⁴

- The safety and adverse events reported in the clinical trial with icatibant compared to standard therapy in patients with ACEI-induced angioedema are reported in the table below.

Adverse Events

Reported Event	Icatibant (N=15)	Standard Therapy (N=15)
Any Adverse Event (AE)	1 (7)	4 (27)
Drug-related AE	1 (7)	1 (7)
Serious AE	0	1 (7)
Injection-site reaction		
Redness	12 (80)	4 (27)
Swelling	8 (53)	3 (20)
Pain	4 (27)	2 (13)
Itching	4 (27)	1 (7)
Sensation of warmth	4 (27)	0

- In the standard therapy group, adverse events included: mild exacerbation of chronic obstructive pulmonary disease (n=1); increase in blood glucose (n=1); fatigue (n=1); influenza-like illness (n=1). This last patient also experience dyspnea, classified as a serious adverse event, of which the patient received rescue therapy with icatibant and prednisolone, with a tracheotomy; the patient was reported to have completely recovered after 20 days.
- Injection site reactions were more common with icatibant compared to standard therapy. Per investigator assessment, all injection site reactions with icatibant resolved within 4 hours; although, two patients reported having an injection-site reaction at 4 hours.

Other Considerations^{3,5-13,15-20}

- When ACEI-induced angioedema is identified, the causative medication should be discontinued.¹⁵ If symptoms do not resolve, patients will often present for emergency treatment and may receive corticosteroids and antihistamines, and epinephrine may also be used in some patients;¹⁵⁻²⁰ however, as mentioned previously, the efficacy of this treatment has been questioned for ACEI-induced angioedema.³ According to several retrospective reviews of patients with ACEI-induced angioedema, overall, approximately 10-15% of patients presenting for emergency management required intubation,¹⁶⁻¹⁹ and 11-40% of patients required admission to the intensive care unit.^{16,17,19,20} In one evaluation, patients presenting with Type 3 angioedema (laryngeal or hypopharyngeal edema) were more likely to be intubated compared to patients with Type 1 angioedema (lip or anterior tongue involvement) (34.1% vs. 0%, respectively; P<0.0001). Approximately 18% of patients with Type 2 angioedema (floor of mouth, palatal, or oropharyngeal edema) required intubation.¹⁸ According to another analysis, pharyngeal swelling (OR 3.6, 95% CI 1.5 to 8.4; P=0.003) and respiratory distress (OR 3.1,

95% CI 1.1 to 8.4; $P=0.03$) were independent predictors of admission to the hospital and increased length of stay, as was race or ethnicity other than white (OR 2.2, 95% CI 1.0 to 4.9; $P=0.49$).²⁰ Similar results were found in patients presenting with angioedema (68.5% ACEI-induced; 31.5% other causes) classified as Type 2 (edema of the floor of the mouth and/or oropharynx, base of the tongue, soft palate, and uvula) or 3 (oropharyngeal edema with involvement of supraglottic and glottic structure), requiring admission to the intensive care unit in 32.1% and 50% of patients, respectively. No patients were intubated that presented with Type 1 angioedema (limited to the face and oral cavity, without involvement of the floor of the mouth), compared to 21.4% for Type 2, and 33.3% Type 3 requiring intubation.¹⁹

- Patients presenting for emergency management of ACEI-induced angioedema may require immediate pharmacologic intervention. There are limited data on the use of agents approved for the management of HAE being used in patients with ACEI-induced angioedema.^{5-13,15} If icatibant is being considered for use, it would need to be readily available at the treating medical center. Icatibant is available for purchase from McKesson without any specialty pharmacy requirements. The shelf-life of icatibant is up to 24 months at 41° F and up to 6 months at 77° F.²¹
- The cost-effectiveness of treatment with icatibant vs. other interventions of patients presenting with severe or life-threatening angioedema has yet to be determined.

Projected Place in Therapy

- Patients with ACEI-induced angioedema should have their ACEI discontinued, with alternate therapy considered and avoidance of reinitiating therapy with an ACEI. Providers should report the adverse reaction by entering the information into CPRS' Allergies/Adverse Reactions field and/or via local reporting mechanisms. Adverse events should also be reported, as appropriate, to the VA ADERS program and FDA MedWatch (1-800-FDA-1088, fax 1-800-FDA-0178, online at <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm>, or by mail).
- Patients presenting with severe symptoms of angioedema, with impending airway compromise should receive supportive care and maintenance of the airway.
- Treatment with icatibant reduced the median time to complete resolution of symptoms in patients presenting to the emergency room with ACEI-induced angioedema of the upper aerodigestive tract (i.e., the face, lips, cheeks, tongue, soft palate or uvula, pharynx, larynx) within 10 hours of onset of the attack, compared to standard therapy with a corticosteroid and antihistamine. Patients in this study appeared to present with more mild to moderate symptoms of angioedema (as noted by patient and investigator assessment); although, three patients in the standard therapy group required rescue therapy (that included icatibant) and one patient required a tracheotomy. As seen in one retrospective evaluation, patients with more mild symptoms did not require intubation, whereas patients presenting with more severe symptoms (e.g., involving laryngeal or hypopharyngeal edema; respiratory distress) are more likely to require intubation. Additional data are needed to determine the overall impact, safety, and cost-effectiveness of icatibant in the management of ACEI-induced angioedema. At present, due to the limited data and off-label use, the need for use of icatibant for ACEI-induced angioedema should be determined on a case by case basis, reserving treatment for patients presenting with more severe symptoms with risk for airway obstruction.

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Appendix A: GRADEing the Evidence

Designations of Quality

<u>Quality of evidence designation</u>	<u>Description</u>
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High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. *Ann Intern Med* 2010;153:194-199.