PRODUCT MONOGRAPH

FIRAZYR®*

icatibant injection
10 mg/mL as icatibant acetate

30 mg/3 mL Single Dose Pre-filled Syringe

Drugs used in hereditary angioedema
ATC Code: B06AC02

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FIRAZYR®
icatibant injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
subcutaneous	Solution /10 mg/mL	none *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

FIRAZYR (icatibant acetate) is indicated for the treatment of acute attacks of hereditary angioedema (HAE) in adults with C1-esterase inhibitor deficiency.

Patients or a caregiver should be trained in subcutaneous injection techniques under the guidance of a healthcare professional before they can administer FIRAZYR (see **Dosage and Administration**).

Geriatrics (> 65 years of age):
Limited information is available regarding the use of FIRAZYR in patients older than 65 years of age (see **Warnings and Precautions** and **Action and Clinical Pharmacology, Pharmacokinetics**).

Pediatrics (<18 years of age):
There are no data to support the use of FIRAZYR in children and adolescents. Repeat administration of icatibant reversibly delayed sexual maturation in rats and dogs (see **Toxicology**).

CONTRAINDICATIONS

Patients who are hypersensitive to icatibant acetate or to any ingredient in the formulation or component of the container. For a complete listing, see **Dosage Forms, Composition and Packaging**.

WARNINGS AND PRECAUTIONS

General

Patients or a caregiver should be trained in subcutaneous injection techniques under the guidance of a healthcare professional before they can administer FIRAZYR. The first administration of FIRAZYR should be performed under the guidance of a healthcare professional before beginning the self-administration of FIRAZYR (see **Dosage and Administration**).

Patients with laryngeal symptoms or any swelling causing breathing difficulties should seek medical attention immediately after administration of FIRAZYR (see **Dosage and Administration**).

Cardiovascular

Ischemic Heart Disease
Icatibant has been shown to aggravate induced cardiac ischemia in several animal models by antagonising the cardioprotective effects of bradykinin (see **Detailed Pharmacology**). Use of icatibant acetate in patients with acute ischemic heart disease or unstable angina pectoris could theoretically lead to a decrease in coronary blood flow and a deterioration in cardiac function.

Stroke
Use of icatibant acetate in the weeks following a stroke could theoretically attenuate the positive late phase neuroprotective effects of bradykinin.

Special Populations

Pregnant Women
No formal studies of the use of FIRAZYR in pregnant women have been conducted. FIRAZYR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal studies showed that icatibant had effects in late stage pregnancy where icatibant exhibited a tocolytic effect resulting in delayed parturition and fetal death at 0.5 and 2-fold the maximum recommended human dose (MRHD) (on an AUC basis at maternal doses of 1 and 3 mg/kg, respectively). Increased fetal distress and perinatal death were observed at high doses (at 7-fold the MRHD, on an AUC basis at a maternal daily dose of 10 mg/kg/day). The potential risk for humans is unknown (see **Toxicology**).

Nursing Women
Animal studies showed that icatibant is excreted in the milk of lactating rats at concentrations similar to those in maternal blood (see **Detailed Pharmacology**). It is unknown whether icatibant is excreted in human breast milk. Many drugs are excreted in human milk, therefore caution should be exercised.

Pediatrics (< 18 years of age)
The safety and efficacy of FIRAZYR in children and adolescents have not been evaluated. Repeat administration of icatibant reversibly delayed sexual maturation in rats and dogs (see **Toxicology**).

Geriatrics (> 65 years of age)
Limited information is available for FIRAZYR in patients older than 65 years of age. Studies demonstrated that the total exposure to icatibant in geriatric patients was higher than in young adults (see **Action and Clinical Pharmacology, Pharmacokinetics**).

Hepatic impairment
Data from subjects with a wide range of hepatic insufficiency suggest that icatibant exposure is not influenced by hepatic impairment. No dosage adjustment is required in patients with hepatic impairment.

Renal impairment
Limited data from subjects with renal insufficiency suggest that icatibant exposure is not influenced by renal impairment. No dosage adjustment is required in patients with renal impairment.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Almost all patients (97%) who were treated with subcutaneous (SC) FIRAZYR in clinical trials developed reactions at the site of injection including erythema, swelling, warm sensation, burning, itching and /or cutaneous pain. These reactions were generally mild to moderate in severity, transient, and the majority (62%) resolved without intervention within 4 hours of FIRAZYR dosing. Other adverse reactions reported by patients treated with FIRAZYR (≥1% to <10% of patients) were dizziness, headache, nausea, rash, erythema, pruritus, pyrexia, and increased transaminase (ALT and AST).

The overall incidence of serious adverse events (SAEs) was low in the clinical development program. In the Phase I and II studies, only 2 SAEs were reported within 14 days of FIRAZYR treatment (manic episode, HAE); these were judged as not related/probably not related to treatment. In the controlled part of the three Phase III studies, only one SAE (cystitis) was reported within 14 days of dosing with FIRAZYR. This event was judged as not related to treatment. In the repeated treatment part of the Phase III studies, safety was evaluated for up to 15 FIRAZYR-treated attacks for patients. Sixteen patients experienced a total of 22 SAEs that occurred within 14 days of FIRAZYR administration. The only SAE that occurred in more than one patient was worsening or recurrence of HAE. Two SAEs were considered by the investigator as related to FIRAZYR treatment (events of arrhythmia and noncardiac chest pain).

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

In all clinical studies, a total of 1,411 HAE attacks have been treated with 30 mg FIRAZYR administered SC.

The safety of FIRAZYR was evaluated in three controlled Phase III trials that included 223 patients who received subcutaneous injection of FIRAZYR 30 mg (n=113), placebo (n=75), or tranexamic acid (n=38), administered by healthcare professionals. Study drug treatment occurred within 6 hours of the attack becoming at least moderate in severity for abdominal or cutaneous attacks. The mean age at study entry was 38 years (range 18 to 83 years), 64% were female, and 95% were Caucasian. Patients were excluded if they were receiving treatment with an angiotensin converting enzyme inhibitor; had evidence of coronary artery disease based on medical history (e.g., unstable angina pectoris, severe coronary heart disease or congestive heart failure [New York Heart Association class 3 and 4]) that in the investigator's judgment would be a contraindication for participation in the trial; or were pregnant or breastfeeding.

The safety data described below represent adverse reactions observed from the two placebo-controlled Phase III trials, consisting of 77 patients who were randomized to receive FIRAZYR at a dose of 30 mg SC, and 75 who were randomized to receive placebo. The safety data represent events occurring within 14 days of treatment of the patient's first attack. The most frequently reported adverse reactions occurring in greater than 2% of FIRAZYR-treated patients (2 or more patients), and at a higher frequency with FIRAZYR compared to placebo, are shown in Table 1. The severity of adverse reactions was assessed by the investigator based on the following definitions: mild - no limitation of usual activities; moderate - some limitation of usual activities; and severe – inability to carry out usual activities. The majority of adverse reactions reported following FIRAZYR treatment were judged to be mild or moderate in severity.

Table 1 - Adverse reactions observed in >2% of FIRAZYR-treated patients (≥2 patients) and at a higher rate with FIRAZYR compared to placebo in the placebo-controlled trials [a]

	FIRAZYR (N = 77) (%)	Placebo (N = 75) (%)
Gastrointestinal disorders		
Abdominal distension	2 (3)	0 (0)
Abdominal pain	2 (3)	0 (0)
Diarrhea	2 (3)	0 (0)
General disorders and administration site conditions		
Injection site reaction[b]	75 (97)	25 (33)
Pyrexia	3 (4)	0 (0)
Infections and infestations		
Nasopharyngitis	2 (3)	0 (0)
Sinusitis	2 (3)	1 (1)
Urinary tract infection	2 (3)	1 (1)
Investigations		
Transaminase increased[c]	3 (4)	0 (0)
Nervous System Disorders		
Dizziness	2 (3)	1 (1)
Respiratory, thoracic and mediastinal disorders		
Nasal congestion	2 (3)	0 (0)

[a] Events occurring within 14 days of study drug administration. Five patients who experienced laryngeal attacks (mild to moderate in severity) were randomized in Study 1 and are included in this table (3 in the FIRAZYR group and 2 in the placebo group); patients with laryngeal attacks were not randomized in Studies 2 and 3 and are excluded from this table.

[b] Injection site reactions include any of the following: injection site burning, injection site erythema, injection site swelling, injection site pain, injection site pruritus, and injection site warmth.

[c] Alanine aminotransferase (ALT), Aspartate aminotransferase (AST)

The third Phase III trial was active-controlled and was comprised of 36 patients who received a single subcutaneous injection of FIRAZYR 30 mg and 38 patients who received the comparator, tranexamic acid. Adverse reactions for FIRAZYR were similar in nature and frequency to those reported in Table 1.

In all three Phase III trials, patients were eligible for FIRAZYR 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 SC at least 6 hours apart for each attack. Across the controlled and open-label phases of the studies, a total of 237 patients were treated with FIRAZYR for at least one acute attack of HAE and 68 were treated for at least 5 attacks. A

limited number of patients experienced up to 15 FIRAZYR-treated attacks. Adverse reactions similar in nature and frequency to those seen in the controlled phase of the trials were observed. Other adverse reactions reported (<5% incidence) included worsening or recurrence of HAE, headache, rash and nausea.

No anaphylactic reactions were reported with FIRAZYR. One patient experienced non-serious adverse reactions of generalized pruritus (moderate in severity) and generalized cutaneous burning sensation approximately 5 hours after injection with FIRAZYR during the patient's eighth treated attack. An antihistamine was administered and the symptoms resolved later that same day. There was no associated rash, no respiratory symptoms or compromise, and no abnormalities in vital signs. There were no similar symptoms or other symptoms related to hypersensitivity during the patient's ninth FIRAZYR-treated attack. At the tenth treated attack, the patient experienced mild generalized pruritus following FIRAZYR administration, which resolved the same day.

In an open-label study, the safety profile of FIRAZYR in patients who self-administered FIRAZYR was similar to that of patients whose therapy was administered by healthcare professionals.

Abnormal Hematologic and Clinical Chemistry Findings

Serum chemistry and hematology parameters were measured at baseline and then at day 2 and day 14 post-treatment during the controlled part of the Phase III studies, and at day 14 post-treatment during the open-label extension phases of these studies.

Liver enzyme tests
Transaminase levels (ALT, AST) were increased in 4% of patients treated with FIRAZYR. See Table 1.

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post-marketing experience with icatibant. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac: Acute myocardial infarction, chest pain.
Investigations: One case of serious AST/ALT increase was reported in a patient with multi-organ failure due to sepsis.

DRUG INTERACTIONS

Overview

Formal drug-drug interaction studies have not been conducted with icatibant acetate. Pharmacokinetic drug interactions involving CYP450 are not expected (see **Action and Clinical Pharmacology**, **Metabolism**). The treatment with FIRAZYR may interfere with the mode of action of angiotensin converting enzyme inhibitor (ACE-I) products.

Drug-Drug Interactions

Table 2 - Established or Potential Drug-Drug Interactions

FIRAZYR	Ref	Effect	Clinical comment
Angiotensin converting enzyme inhibitor (ACE-I) products	T	Co-administration of FIRAZYR and ACE-I is not expected to lead to changes in blood or tissue levels of either medicinal product. A theoretical mode of action for ACE-I in treatment of cardiac indications is the increase of systemic bradykinin. Thus, treatment with FIRAZYR may interfere with the mode of action of ACE-I products by blocking the bradykinin 2 receptor. FIRAZYR has been reported to attenuate the blood pressure-lowering effects of ACE-I in normotensive and hypertensive subjects.	Caution is recommended if FIRAZYR is administered concomitantly with ACE-I products.

Legend: T = Theoretical

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

FIRAZYR may have an influence on the ability to drive or use machines. Fatigue, lethargy, tiredness, somnolence, and dizziness have been reported following the use of FIRAZYR. These

symptoms may occur as a result of an attack of HAE. Patients should be advised not to drive or use machines if they feel tired or dizzy.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

The recommended dose of FIRAZYR is 30 mg administered by slow subcutaneous injection in the abdominal area. Additional doses may be administered at intervals of at least 6 hours if response is inadequate or if symptoms recur. No more than 3 doses may be administered in any 24 hour period. The safety of more than 8 injections in a month has not been investigated in clinical trials.

Missed Dose

Not applicable.

Administration

FIRAZYR is supplied as a single-dose pre-filled syringe that delivers 3 mL of solution, equivalent to a 30 mg icatibant acetate dose. Each syringe and needle are for single-use only and should be discarded in a sharps container after use.

FIRAZYR is not to be injected if the patient has only pre-attack symptoms (e.g. paresthesia or erythema).

FIRAZYR should be inspected visually for particulate matter and discoloration prior to administration. The drug solution should be clear and colorless. Do not administer if the product contains particulates or is discolored.

Attach the provided 25 gauge needle to the syringe hub and screw on securely. Do not use a different needle. Disinfect the injection site and administer FIRAZYR by subcutaneous injection in the abdominal area over at least 30 seconds.

Patients (or their caregivers) may self-administer FIRAZYR upon recognition of symptoms of an HAE attack. They should be trained in subcutaneous injection techniques by a healthcare professional before they can administer FIRAZYR. The first administration of FIRAZYR should be performed under the guidance of a healthcare professional before beginning the self-administration of FIRAZYR.

Self-administration training is also available to patients directly through Shire's HAE Patient Support Program.

Patients with laryngeal symptoms or any swelling causing breathing difficulties should seek medical attention immediately after administration of FIRAZYR and need to be managed in an appropriate medical institution after injection until the physician considers discharge to be safe.

Pediatric Population
The safety and efficacy of FIRAZYR in children 0-18 years of age have not been established.

Elderly Patients
Patients >65 years of age are likely to have increased systemic exposure to FIRAZYR compared to younger patients. The magnitude of these differences is not expected to be clinically relevant for safety or efficacy, and therefore no dose adjustment is necessary for elderly patients.

Patients with Hepatic Impairment
No dosage adjustment is required.

Patients with Renal Impairment
No dosage adjustment is required.

OVERDOSAGE

In a clinical study evaluating a 90 mg dose (30 mg in each of 3 subcutaneous sites), the adverse event profile was similar to that seen with 30 mg administered in a single subcutaneous site.

In another clinical study, a dose of 3.2 mg/kg intravenously (approximately 8 times the therapeutic dose) caused transient erythema, itching or hypotension in healthy subjects. No therapeutic intervention was necessary.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Hereditary angioedema (HAE) types I and II is an autosomal dominant disease. It is caused by absence or dysfunction of C1-esterase-inhibitor, a key regulator of the Factor XII/kallikrein proteolytic cascade, that leads to bradykinin production. Bradykinin is a vasodilator which is the key mediator of the characteristic HAE symptoms of localized swelling, inflammation and pain. An HAE attack usually lasts between 2 to 5 days.

Icatibant is a competitive antagonist selective for the bradykinin B2 receptor, with an affinity similar to bradykinin and thereby treats the clinical symptoms of an acute, episodic attack of HAE (see **Detailed Pharmacology**).

Pharmacodynamics

Following bradykinin challenge, development of bradykinin-induced hypotension, vasodilation, and reflex tachycardia was prevented in healthy young subjects who received doses of 0.8 mg/kg over 4 hours, 1.5 mg/kg/day or 0.15 mg/kg/day for 3 days. Icatibant was shown to be a competitive antagonist when the bradykinin challenge dose was increased 4-fold. Doses of 0.4 and 0.8 mg/kg inhibited response to challenge with bradykinin for 6 to 12 hours after the infusion was initiated.

Cardiac Electrophysiology

In a randomized, placebo- and positive-controlled, crossover ECG assessment study in healthy subjects (N=70), single subcutaneous doses of icatibant 30 mg (therapeutic dose) and 90 mg (3X supratherapeutic dose) were not associated with effects on the QTc interval, the QRS duration, the PR interval, or heart rate.

Pharmacokinetics

Table 3 - Summary of Icatibant's Pharmacokinetic Parameters in Healthy Subjects Following SC Administration

	C_{max}	$t_{½}$ (h)	AUC_{0-4}	Clearance	Volume of distribution
Single dose mean (30 mg/kg)	974 ± 280 ng/mL	1.4 ± 0.3hours	2165 ± 568 ng·hr/mL	245 ± 58 mL/min	29.0 ± 8.7 L

Absorption

Following subcutaneous administration of a single 30 mg dose of FIRAZYR to healthy subjects (N=96), a mean (± standard deviation) maximum plasma concentration (C_{max}) of 974 ± 280 ng/mL was observed after approximately 0.75 hours. The mean area under the plasma concentration-time curve ($AUC_{0-\infty}$) after a single 30 mg dose was 2165 ± 568 ng·hr/mL, with no evidence of accumulation of icatibant following three 30 mg doses administered 6 hours apart.

Distribution

Following subcutaneous administration of a single 30 mg dose the volume of distribution at steady state (V_{ss}) was 29.0 ± 8.7 L.

Metabolism

Icatibant is extensively metabolized by proteolytic enzymes to inactive metabolites. Icatibant is not degraded by oxidative metabolic pathways, is not an inhibitor of major cytochrome P450 (CYP) isoenzymes (CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4) and is not an inducer of CYP 1A2 and 3A4.

Excretion

Following subcutaneous administration of a 30 mg dose, plasma clearance was 245 ± 58 mL/min with a mean elimination half-life of 1.4 ± 0.4 hours.

Inactive metabolites are primarily excreted in the urine, with less than 10% of the dose eliminated as unchanged drug.

Special Populations and Conditions

Body weight
The plasma clearance was higher in patients with increased body weight.

Geriatrics
Elderly patients (>65 years of age) have been shown to have increased systemic exposure to icatibant.

Hepatic and Renal Insufficiency
Clinical pharmacokinetic studies demonstrate that for mild to moderate impairment of renal or hepatic function, no dose adjustment is necessary. In 10 patients with hepatorenal syndrome (GFR 30-60 mL/min), clearance of icatibant was not dependent on renal function. Icatibant clearance in subjects with a wide range of hepatic impairment (Child-Pugh score ≥ 7 and ≤ 15) was similar to that of healthy subjects.

Pediatrics
There are no pharmacokinetic data in children.

STORAGE AND STABILITY

Store at 2-25° C; do not freeze.

SPECIAL HANDLING INSTRUCTIONS

The solution should be clear and colorless and free from visible particles. Pre-filled syringes are for single use only. Any unused product or waste materials should be disposed of in accordance with local requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

FIRAZYR is supplied as a sterile solution for subcutaneous injection in a single use pre-filled syringe. The solution is clear and colorless.

Each pre-filled syringe delivers 3 mL containing icatibant acetate equivalent to 30 mg icatibant. Each mL of the solution contains 10 mg of icatibant. Each mL of solution contains the nonmedicinal ingredients acetic acid glacial, sodium chloride, sodium hydroxide, and water for injection.

3 mL of solution is supplied in a 3 mL pre-filled syringe (clear type I glass) with grey plunger stopper (bromobutyl coated with fluorocarbon polymer), a Luer-lock with a screw tip cap, and a white polypropylene backstop. A hypodermic needle (25 G; 16 mm) is included in the pack.

Pack includes one pre-filled syringe with one needle.

A patient self-administration kit, containing a travel case, needle protection devices and alcohol wipes can also be obtained through Shire's HAE patient support program.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

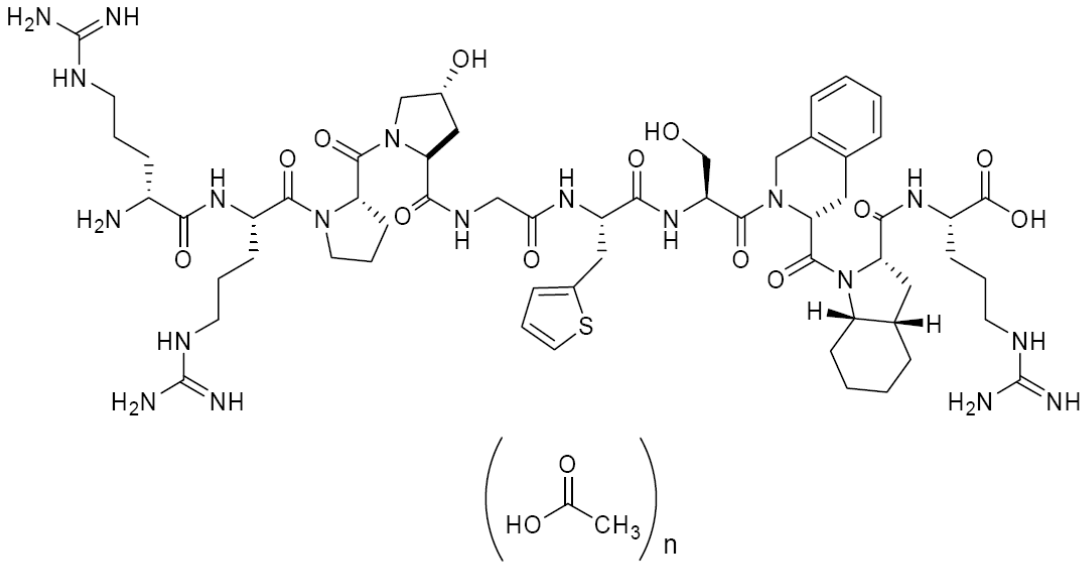
Drug Substance

Common name: icatibant acetate

Chemical name: D-Arginyl-L-arginyl-L-prolyl-L[(4R)-4-hydroxyprolyl]-glycyl-L[3-(2-thienyl)alanyl]-L-seryl-D-(1,2,3,4-tetrahydroisoquinolin-3-ylcarbonyl)-L[(3aS,7aS)-octahydrindol-2-ylcarbonyl]-L-arginine, acetate salt

Molecular formula and molecular mass: $C_{59}H_{89}N_{19}O_{13}S$ (net), 1304.55 g/mol (average, net)

Structural formula:



Physicochemical properties: FIRAZYR (icatibant) is a synthetic decapeptide with five non-proteinogenic amino acids.

Solubility properties: Icatibant acetate is soluble in water, isotonic saline, phosphatebuffer (pH 7.4), acetate buffer (pH 3.5), Tris buffer, ethanol,and methanol.

CLINICAL TRIALS

Study demographics and trial design

Table 4 - Summary of patient demographics for clinical trials in HAE

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Study 1 (FAST 3, HGT-FIR-054)	Randomized, placebo-controlled, parallel-group: Patients with moderate to severe cutaneous or abdominal attacks or mild to moderately severe laryngeal attacks	FIRAZYR 30mg/3mL SC x 1 dose or placebo 3mL SC x 1 dose.	93	36.8 years (18 to 83)	34 male; 59 female
	Open-label: Patients with severe laryngeal attack	FIRAZYR 30mg/3mL SC x 1 dose.	5	41.6 years (29 to 59)	3 male; 2 female
	Open-label extension: Patients with subsequent attacks	FIRAZYR 30mg/3 mL SC for up to 3 doses at least 6 hours apart.	82	37.2 years (18 to 83)	27 male; 55 female
	Entire Study		98	37.0 years (18 to 83)	37 male; 61 female
Study 2 (FAST 1, JE049 #2103)	Randomized, double-blind, placebo-controlled: Patients with moderate to severe abdominal or cutaneous attacks	FIRAZYR 30mg/3mL SC x 1 dose. or placebo 3mL SC x 1 dose.	56	34.9 years (18 to 58)	19 male; 37 female
	Open-label: Patients with any laryngeal attack	FIRAZYR 30mg/3mL SC x 1 dose.	8	47.1 years (25 to 61)	3 male; 5 female
	Open-label extension: Patients with subsequent attacks	FIRAZYR 30mg/3mL SC for up to 3 doses at least 6 hours apart.	72	35.5 years (18 to 65)	23 male; 49 female
	Entire Study		84	36.6 years (18 to 65)	27 male; 57 female

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Study 3 (FAST 2, JE049 #2102)	Randomized, double-blind, active- controlled: Patients with moderate to severe abdominal or cutaneous attacks	FIRAZYR 30mg/3mL SC x 1 dose or tranexamic acid PO TID for 2 days plus a placebo matched to the alternate therapy.	74	41.1 years (19 to 68)	27 male; 47 female
	Open-label: Patients with any laryngeal attack	FIRAZYR 30mg/3mL SC x 1 dose.	3	35.0 years (27 to 48)	2 male; 1 female
	Open-label extension: Patients with subsequent attacks	FIRAZYR 30mg/3mL SC for up to 3 doses at least 6 hours apart.	54	42.3 years (22 to 70)	19 male; 35 female
	Entire Study		85	40.9 years (19 to 70)	30 male; 55 female
Study 4 (JE049-3101)	Open-label, uncontrolled	FIRAZYR 30mg/3mL SC x 1 dose.	104	41.6 years (18 to76)	36 male; 68 female
	HCP Administration: Any attack severe enough to warrant treatment.		23	44.0 years (19 to 76)	8 male; 15 female
	Self-administration: Any attack severe enough to warrant treatment		98	40.8 years (18 to 76)	33 male; 65 female

SC=subcutaneous; HCP=Healthcare professional

The efficacy and safety of FIRAZYR for the treatment of acute attacks of HAE in adults was established by three controlled Phase III clinical trials (designated Study 1, 2, and 3). In these studies, patients were enrolled if their attack involved the cutaneous, abdominal and/or laryngeal areas; the cutaneous or abdominal attacks were at least moderate in severity and the laryngeal attacks were at least mild in severity, as determined by the investigator; and study drug could be administered within 6 hours of the attack severity becoming at least mild (laryngeal) or moderate (non-laryngeal), but not more than 12 hours after the onset of the attack.

The phase III clinical trials used endpoints that were specifically developed to assess the response to therapy in patients with acute HAE attacks. The effect of therapy on HAE-specific symptoms was recorded by the patients using a visual analog scale (VAS) during pretreatment and at pre-determined time points after administration of therapy. The symptoms assessed by the patient

using the VAS were skin swelling, skin pain, and abdominal pain. Patients with laryngeal attacks also assessed difficulty swallowing and voice change.

Study 1was a randomized, double-blind, placebo-controlled study of 98 adult HAE type I or II patients with a mean age of 37.0 years (88.8% white; 86.7% HAE type I; 3.1% >65 years of age) who had developed moderate to very severe cutaneous or abdominal, or mild to moderately severe laryngeal attacks of HAE. These patients were randomized to receive a single dose of either FIRAZYR 30 mg or placebo by SC injection. Patients with severe laryngeal attacks of HAE were not randomized and received open-label FIRAZYR 30 mg SC. In the open-label extension phase of the study, patients were eligible for treatment of subsequent attacks with FIRAZYR 30 mg SC and could receive up to 3 doses at least 6 hours apart for each attack.

The primary endpoint of Study 1 was the Time to Onset of Symptom Relief (TOSR), assessed using a 3-item composite visual analog scale score (VAS-3) consisting of assessments of skin swelling, skin pain and abdominal pain. The non-laryngeal ITT population was used for the primary efficacy analysis. The onset of symptom relief was defined as a 50% reduction from pretreatment in the composite VAS score. The time of onset of symptom relief was determined retrospectively as the earliest of 3 consecutive non-missing measurements for which there was at least a 50% reduction in the pretreatment composite VAS score.

Studies 2 and 3 were randomized, double-blind, controlled trials and had identical designs except for the comparator. In Study 2 an attack of HAE was treated with a single dose of either FIRAZYR 30 mg, or placebo administered by SC injection. Study 3 was designed as a double-blind, double-dummy trial with tranexamic acid as an active comparator. Tranexamic acid tablets were encapsulated and oral placebo consisted of capsules of identical size, shape and color. Initial treatment of the attack in the double-blind phase consisted of 1 SC injection of FIRAZYR administered with 2 capsules of placebo (oral) or 1 SC injection of placebo administered with 2 capsules of tranexamic acid (oral). Subsequent study drug treatment consisted of tranexamic acid or matching placebo administered orally (3 times per day) for 2 days.

In Studies 2 and 3, patients who developed moderate to very severe cutaneous or abdominal attacks of HAE were eligible for randomization to study drug treatment; patients with laryngeal symptoms were not randomized and were treated with open-label FIRAZYR 30 mg SC. Similar to Study 1, both studies had open-label extension phases in which patients were eligible for treatment of subsequent attacks with FIRAZYR (30 mg SC for up to 3 doses administered at least 6 hours apart).

The primary efficacy endpoint for Studies 2 and 3 was the Time to Onset of Primary Symptom Relief based on a pre-specified reduction from the pretreatment VAS score for a single identified primary symptom. The primary symptom was identified based on the type of attack. For abdominal attacks, the single primary symptom was based on the VAS for “abdominal pain.” For cutaneous attacks, the single primary symptom was based on the most severe VAS for “skin swelling” or “skin pain.” If both were equally severe, the VAS for “skin pain” was used. This endpoint was defined as the key secondary efficacy endpoint for Study 1. The non-laryngeal ITT population was used for the primary efficacy analyses of both studies.

Study 2 enrolled 84 adult HAE type I or II patients with a mean age of 36.6 years (95.2% white; 84.5% HAE type I; 0% >65 years of age). Study 3 enrolled 85 adult HAE type I or II patients with a mean age of 40.9 years (100% white; 91.8% HAE type I; 4.7% >65 years of age).

Study results

Double-blind, Controlled Trials

Efficacy results are shown in Figure 1 and Table 5 below.

Figure 1 Time to 50% reduction from baseline 3-item VAS score in Study 1 (non-laryngeal ITT population)

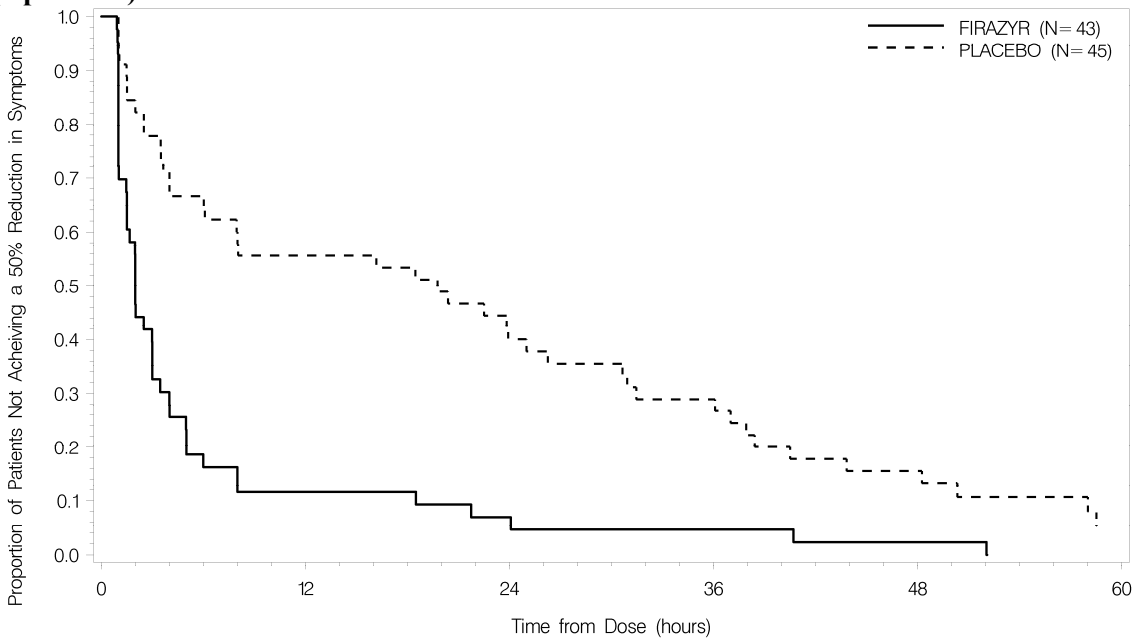


Table 5 - Results of studies 1, 2, and 3 in the non-laryngeal ITT population

Study 1	**Statistic**	**FIRAZYR (n = 43)**	**Placebo (n = 45)**
Primary Endpoint			
Time to Onset of Symptom Relief (hours) [a]	Median p-value	2.0 < 0.001	19.8
Other Endpoints			
Time to Onset of Primary Symptom Relief (hours) [b]	Median p-value	1.5 < 0.001	18.5
Time to Onset of Symptom Relief (hours) for the Individual VAS score of [c]			
Skin Swelling	Median p-value	3.0 <0.001	22.3

Skin Pain	Median p-value	2.0 0.013	8.0
Abdominal Pain	Median p-value	1.8 0.007	3.5
Change in Composite VAS Score at 2 hours After Treatment	Mean p-value	-19.74 <0.001	-7.49
Time to Almost Complete Symptom Relief (hours) [d]	Median p-value	8.0 0.012	36.0
Patients who use Rescue Medication Prior to Onset of Symptom Relief	Number (%) p-value	0/43 (0%) <0.001	16/45 (35.6%)
Study 2	**Statistic**	**FIRAZYR (n = 27)**	**Placebo (n = 29)**
Primary Endpoint			
Time to Onset of Primary Symptom Relief (hours) [b]	Median p-value	2.5 0.142	4.6
Other Endpoints			
Time to Onset of Symptom Relief (hours) [a, e]	Median p-value	2.3 0.014	7.9
Time to Almost Complete Symptom Relief (hours)[d]	Median p-value	8.5 0.079	19.4
Patients who used Rescue Medication Prior to Onset of Symptom Relief[e, f]	Number (%) p-value	1/26 (3.8) 0.005	10/27 (37.0)
Study 3	**Statistic**	**FIRAZYR (n = 36)**	**Tranexamic Acid (n=38)**
Primary Endpoint			
Time to Onset of Primary Symptom Relief (hours)[b]	Median p-value	2.0 < 0.001	12.0
Other Endpoints			
Time to Onset of Symptom Relief (hours)[a e]	Median p-value	2.0 < 0.001	12.0
Time to Almost Complete Symptom Relief (hours) [d]	Median p-value	10.0 <0.001	51.0
Patients who used Rescue Medication Prior to Onset of Symptom Relief[e, f]	Number (%) p-value	0/33 (0) 0.002	9/34 (26.5)

[a]Onset ofsymptom relief was defined as the earliest of 3 consecutive non-missing measurements for which there was at least a 50% reduction from pretreatment composite 3-item (skin swelling, skin pain, and abdominal pain) VAS score.
[b] Primary symptom relief was defined as a reduction from pretreatment in the score of a single primary VAS Symptom. Onset of symptom relief was defined as the earliest of 3 consecutive non-missing measurements for which there was any reduction below (6/7) pre-treatment value – 16 for pretreatment VAS ≥30mm. For a pre-treatment VAS < 30mm, symptom relief was defined as a 68% reduction from pre-treatment.
[c] Onset of symptom relief (hours) for the individual VAS scores was defined as the earliest of 3 consecutive non-missing measurements for which there was at least a 50% reduction from the pretreatment VAS score for each of the individual symptoms.
[d]Almost complete symptom relief (hours) was defined as the earliest of 3 consecutive non-missing measurements for which all VAS scores were less than 10 mm.
[e] Post-hoc analysis
[f] Analysis includes only those subjects who achieved onset of symptom relief; Study 2: FIRAZYR n=26, Placebo n=27; Study 3: FIRAZYR n= 33, Tranexamic Acid n=34.

Response was also consistent across repeated attacks in the controlled Phase III trials. A total of 237 patients were treated with 1,383 doses of 30 mg FIRAZYR for 1,278 attacks of acute HAE in these Phase III clinical trials. Ninety-one and one-half percent (91.5%) of attacks of HAE that were eligible for 3 injections (1149) were treated with a single dose of FIRAZYR. In the first 15 FIRAZYR treated attacks (1,114 doses for 1,030 attacks), the median times to onset of symptom relief were similar across attacks (2.0 to 2.5 hours).

Patients with laryngeal attacks were treated during the open-label phases of the studies, therefore comparisons of the efficacy of FIRAZYR with a control arm are not available for most of the patients with laryngeal attacks. In study 1, 27 patients completed laryngeal symptom assessments using a 5-item composite visual analog score (VAS-5). Post-hoc analyses of these efficacy data are shown in Table 6 below. The median time to onset of symptom relief (2.0 hours) was similar to those observed for the non-laryngeal attacks in studies 1, 2 and 3 (2.0 to 2.3 hours). This was reflected by similar median times to onset of symptom relief for the individual laryngeal symptoms of difficulty swallowing (1.8 hours) and voice change (1.7 hours). No formal studies have been conducted to determine if Firazyr treatment can reduce the risk of suffocation and mortality in HAE patients with laryngeal attacks.

Table 6 - Results of Study 1 in the laryngeal treated population (post-hoc analysis)

Endpoints	Statistic	FIRAZYR (n = 27)
Time to onset of symptom relief (hours) [a]	Median (95% CI)	2.0 (1.5, 3.5)
Time to Onset of Primary Symptom Relief (hours) [b]	Median (95% CI)	2.0 (1.5. 2.5)
Time to Onset of Symptom Relief (hours) for the Individual VAS score of [c]		
Difficulty Swallowing	Median (95% CI)	1.8 (1.3, 2.5)
Voice Change	Median (95% CI)	1.7 (1.5, 2.5)
Skin Swelling	Median (95% CI)	1.8 (1.3, 5.0)
Skin Pain	Median (95% CI)	1.8 (1.3, 3.5)
Abdominal Pain	Median (95% CI)	2.2 (1.0, 48.4)
Time to Almost Complete Symptom Relief (hours) [d]	Median (95% CI)	6.4 (3.1, 24.3)

[a] Onset of symptom relief was defined as the earliest of 3 consecutive non-missing measurements for which there was at least a 50% reduction from pretreatment composite 5-item (difficulty swallowing, voice change, skin swelling, skin pain, and abdominal pain) VAS score.

[b] Primary symptom relief was defined as a reduction from pretreatment in the score of a single primary VAS Symptom. Onset of symptom relief was classified as the ealiest of 3 consecutive non-missing measurements for which there was any reduction below (6/7) pre-treatment value – 16 for pretreatment VAS ≥30mm. For a pre-treatment VAS < 30mm, symptom relief was defined as a 68% reduction from pre-treatment. For the laryngeal attacks, the single primary symptom was based on the more severe pretreatment VAS score of either difficulty swallowing or voice change. If both were equally severe at pretreatment, then the VAS score for difficulty swallowing was used as the single primary symptom.

[c] Onset of symptom relief (hours) for the individual VAS scores was defined as the earliest of 3 consecutive non-missing measurements for which there was at least a 50% reduction from the pretreatment VAS score for each of the individual symptoms.

[d] Almost complete symptom relief (hours): was defined as the earliest of 3 consecutive non-missing measurements for which all VAS scores were less than 10 mm.

Open-label, Uncontrolled Study

Self-administration of FIRAZYR by patients who experienced acute attacks of HAE was assessed in the open-label uncontrolled Study 4. Patients who self-administered FIRAZYR during an acute attack of HAE had results similar to those seen after administration by a healthcare professional in the controlled Phase III studies.

DETAILED PHARMACOLOGY

Icatibant is a potent antagonist of the bradykinin (B2) receptors with an affinity similar to bradykinin itself. Receptor binding of icatibant has been demonstrated in various tissues and cells in vitro, including guinea pig ileum and tracheal epithelial cells, human synovial cells and human recombinant CHO cells.

In bradykinin type-1 (B1) receptor binding assays in vitro using human recombinant CHO cells, the half-maximal inhibitory concentration (IC_{50}) of icatibant was determined to be 6 μM, with an inhibition constant (K_i) of 1.2 μM. In binding to the B2 receptor, the IC_{50} of icatibant was 4.3 nM, and the K_i was 2.0 nM. Selectivity for the B2 receptor was also demonstrated in vitro by the inability of icatibant to inhibit contractions of rabbit aorta, which contains the B1 receptor, induced by the B1 agonist, des-Arg10-kallidin.

The B2 receptor has been implicated in the cardioprotective effects of bradykinin, and antagonism of this receptor could potentially have negative cardiovascular effects during reperfusion after acute ischemia. Icatibant decreased coronary blood flow in the isolated guinea pig heart and aggravated the duration of post-ischemic reperfusion arrhythmias in the isolated rat heart. Intracoronary infusion of icatibant in an anesthetized myocardial infarction dog model increased mortality rate 2-fold over saline infusion. Icatibant does not cause cardiac conduction changes in vitro using the *Xenopus* oocyte model, nor does it have significant effects on HERG-mediated outward current in CHO cells at concentrations up to 300 μM. Icatibant did not elicit any cardiac conduction changes or in vivo in normal dogs or in various dog models (ventricular pacing, physical exertion and coronary ligation) where no associated hemodynamic changes were observed.

Based on animal data there is a theoretical potential that antagonism of the B2 receptor can lead to myocardial ischemia. Myocardial ischemic events have been reported infrequently in post-marketing experience with Firazyr but there is no clear evidence that such events were related to product use. Overall, there is limited human experience in acute ischemia. Prescribers should consider benefits and risks of therapy.

Absorption, distribution, metabolism, and excretion studies have been performed in mice, rats, and dogs. Two inactive metabolites, M1 and M2, have been isolated, identified, and found to be similar across species. Excretion of radioactivity was mainly renal, regardless of species and route of administration. Based on the pharmacokinetic data generated in these studies, including maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC), the absolute bioavailability of icatibant following SC administration is high (approximately 100%). Subcutaneous administration studies indicated a biphasic decline of radioactivity in blood, initially rapid (1 to 2 hours post-dose), followed by a second phase lasting days.

Icatibant and its metabolites M1 and M2 were tested for in vitro metabolic stability in the presence of human liver microsomes and (for icatibant only) in the presence of dog liver microsomes as well as dog and human S9-fractions. In vitro studies investigating effects on human cytochrome P450 (CYP) enzymes did not show any induction or inhibition. The data from these studies showed that the metabolism of icatibant, M1, and M2 is CYP-independent.

Icatibant is excreted in the milk of lactating rats at concentrations similar to those in maternal blood.

Symptoms consistent with histamine release have been observed in dogs after IV administration of icatibant, where the ears and muzzle became swollen. These nonclinical study data help explain the mechanisms underlying the adverse localized cutaneous reactions observed at injection sites in humans.

Broad receptor binding, using standard agonists, has been investigated for icatibant and its two major metabolites (M1 and M2). Inhibition by icatibant was detected for the following humanized receptors: B2 (percent of control specific binding 98%), M_3 (52%), M_4 (16%), NK_2 (96%), opiate (19%), EP_1 (13%), VIP_1 (56%), VIP_2 (41%), and V_{1a} (66%) receptor. The IC_{50} value of icatibant for the binding at NK2 receptors was 420 nM, which is approximately 100-fold higher than the IC_{50} value for the B2 receptor. Partial inhibition of control specific binding was observed for M2 at the B2 (62%) receptor only, at concentrations of 10 μM-approximately 10 times the C_{max} in human following SC administration of icatibant with no inhibition observed with M1.

TOXICOLOGY

Long-term multidose (Repeat dose) Studies

Repeated-dose studies have been conducted in rats and dogs for durations of 6 and 9 months, respectively. In both rats and dogs, there was a dose-related reduction in circulating sex hormone levels.

In the mature rat, ovary weights were increased in females and prostate weights decreased in males. With the exception of the spleen weights (increased), these changes in organ weights were completely or partially reversed following the dose-free recovery period. Histopathological changes of the reproductive organs in the males included minimal to severe bilateral hypospermia and minimal or slight intratubular degenerate spermatozoa/spermatids in the epididymides, minimal or moderate reduction in secretion in the prostate gland and seminal vesicles, minimal to marked bilateral germinal epithelial degeneration in the testes in males. In the females, changes included masculinization of the mammary glands, increased numbers of corpora lutea and decreased developing follicles in the ovaries, minimal to marked uterine atrophy and mucification and/or atrophy of the vaginal mucosa. Microscopic findings in reproductive organs of male and female animals included severe bilateral tubular atrophy of the testes, atrophy and inactivation of the mammary glands, severe atrophy of the prostate gland, slight to moderate uterine atrophy, no corpora lutea or developing follicles in the ovaries and absence of spermatozoa in the epididymal tubules. Following the 4-week recovery period, most findings showed evidence of at least partial recovery.

In the mature dog, testosterone levels in males were lowered in the majority of animals. FSH levels (both sexes) showed a trend toward decrease. These findings were reversible following the 4 week treatment-free period.

Repeat use of icatibant reversibly delayed sexual maturation of juvenile rats and dogs. Sexually immature rats were treated daily with 3 mg/kg for 7 weeks. Macroscopic observations in the male rats included atrophy of testes and epididymides. Microscopic findings of tubular cell vacuolation and germ cell degeneration in the testes were observed. In the males treated with 9.0 and 25 mg/kg/day, there was statistically significant delays in physical maturation, lowered prostate and testes weights, tubular cell vacuolation and germ cell degeneration. Decreased sperm count, motility, and velocity were observed when males were treated with the dose of 25 mg/kg/day. Consequently, decreased fertility was observed in untreated females paired with males treated with an icatibant dose of 25 mg/kg/day. All microscopic and organ weight findings were either completely or partially reversible following the treatment-free period. In the females, there was reduced uterine weight.

Sexually immature dogs were treated with icatibant for 13-weeks. The observations in the male dogs included lower testicular volume, lower testosterone, LH (males) and FSH levels. In the female dogs, the FSH levels were lower. These effects showed partial reversibility during the treatment-free period. Macroscopic observations included decreased testes, epididymides, prostate, uterus, vagina and ovaries. Immaturity of the genital organs was observed in all males at all dose levels as well as in the females, which also demonstrated lack of glandular portion of the mammary glands. During the treatment-free period, progressive development and maturation of the male and female reproductive organs was considered to be consistent with the normal maturation process and recovery.

The observations regarding the reproductive organs in the sexually immature animals are similar to the effects of icatibant on reproductive tissues in sexually mature rats and dogs (see above). Icatibant has a reversible effect on the gonadotrophins.

Bradykinin, acting through the B2 receptor, is recognized to have a role in the control of hormone secretion within the hypothalamus. Therefore, these effects on hormone secretion, with consequent effects on sexual organs, are not unexpected. The daily dosing regimen utilized in the nonclinical studies is an exaggeration of the clinical treatment conditions. Adult patients treated with icatibant are unlikely to experience adverse reactions affecting sexual organs, given the intermittent nature of HAE attacks and use of icatibant.

In a clinical setting, 39 healthy adult men and women were treated with a single SC 30 mg injection every 6 hours for 3 doses every 3 days for a total of 9 doses. There were no clinically significant changes from baseline in basal and GnRH-stimulated concentrations of reproductive hormones (estradiol, progesterone, prolactin, DHEA, DHEAS, SHBG, FSH, and LH) in females and (testosterone, DHEA, DHEA-S, SHBG, FSH, LH, and Inhibin-B) in males. There were no significant effects of icatibant on the concentration of luteal phase progesterone and luteal function, or on menstrual cycle length in females, and there were no significant effects of icatibant on sperm count, motility and morphology in males. The dosing regimen used for this study is very unlikely to be sustained in the clinical setting.

Carcinogenicity
A two-year study was conducted in rats to assess the carcinogenic potential of icatibant. No evidence of tumorigenicity was observed in rats at icatibant subcutaneous doses up to 6 mg/kg/day (approximately 6-fold greater than the Maximum Recommended Human Dose on an AUC basis).

Genotoxiciy
In a standard battery of in vitro and in vivo tests, icatibant was not genotoxic.

Developmental and Reproductive Studies
Icatibant was not teratogenic when administered by subcutaneous injection during early embryonic and fetal development in rat (25 mg/kg/day) and rabbit (10 mg/kg/day). In animal studies, icatibant caused delayed parturition, fetal death, and pre-implantation loss in rats and premature birth, abortion, fetal death, and pre-implantation loss in rabbits. Delayed parturition and fetal death in rats occurred at 0.5 and 2-fold, respectively, the maximum recommended human dose (MRHD) (on an AUC basis at maternal doses of 1 and 3 mg/kg, respectively). Increased pre-implantation loss in rats occurred at 7-fold the MRHD (on an AUC basis at a maternal daily dose of 10 mg/kg). The mean number of pups born per female was lower than for the controls and pup survival rate (10 mg/kg/day) was 25% between day 1 and day 4 post-partum. After day 4 post-partum, pup survival was 100%.

Studies in rabbits indicated that pre-implantation loss and increased fetal deaths occurred at 13-fold greater than the MRHD (on an AUC basis at a maternal dose of 10 mg/kg). Icatibant is a potent antagonist of bradykinin and therefore, at high dose levels, treatment can have effects on the uterine implantation process and subsequent uterine stability in early pregnancy. These uterine effects also manifest in late stage pregnancy where icatibant exhibits a tocolytic effect resulting in delayed parturition in the rat, with increased fetal distress and perinatal death at high doses (10 mg/kg/day).

Following a single SC dose (1 mg/kg) to pregnant rats, no effects were detected in the post-natal development of rat pups.

PART III: CONSUMER INFORMATION

PrFIRAZYR®*
icatibant injection

This leaflet is part III of a three-part "Product Monograph" published when FIRAZYR was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about FIRAZYR. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
FIRAZYR is used for treating acute attacks of hereditary angioedema (HAE) in adults with a deficiency of a protein called C1-esterase inhibitor.

What it does:
In HAE, levels of a substance in your bloodstream called bradykinin are increased leading to symptoms like swelling, pain, nausea, and diarrhea. FIRAZYR blocks the activity of bradykinin and ends further progression of the symptoms of an HAE attack.

When it should not be used:
Do not use FIRAZYR if you are allergic to icatibant or any other ingredients in FIRAZYR or the container.

What the medicinal ingredient is:
Icatibant acetate

What the nonmedicinal ingredients are:
acetic acid glacial, sodium chloride, sodium hydroxide, and water for injection.

What dosage forms it comes in:
FIRAZYR is a solution for subcutaneous injection containing 10 mg/mL icatibant as acetate. FIRAZYR is available in a single dose pre-filled syringe containing 30 mg/3mL icatibant as acetate. A patient self-administration kit, containing a travel case, needle protection devices and alcohol wipes can also be obtained through Shire's HAE support program.

WARNINGS AND PRECAUTIONS

You or your caregiver should receive proper training from a healthcare professional on how to give subcutaneous (under the skin) injections of FIRAZYR.

If you have a laryngeal attack (obstruction of the upper airway causing difficulty breathing) inject FIRAZYR and then go to the emergency room of the nearest hospital for medical help right away.

BEFORE you use FIRAZYR talk to your doctor or pharmacist if you:

- have heart problems such as unstable angina (reduced blood flow to the heart muscle)
- have recently suffered a stroke
- are pregnant or plan to become pregnant
- are breastfeeding

FIRAZYR is not recommended for use in patients under 18 years of age.

Driving and Using Machinery
FIRAZYR may cause tiredness, dizziness or sleepiness. DO NOT drive or operate machinery after using FIRAZYR if you feel tired or dizzy.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist about all of the medicines you take, including the ones you can buy without prescription, vitamins, and natural health products.

FIRAZYR may affect how an angiotensin converting enzyme (ACE) inhibitor works. An ACE inhibitor is used to lower blood pressure.

PROPER USE OF THIS MEDICATION

A healthcare professional may give you your first dose of FIRAZYR injection, then tell you when it is safe to go home.

A healthcare professional will also teach you how to safely inject FIRAZYR before you can give yourself an injection.

You should be able to read and follow step-by-step instructions for injection provided under the heading "Step-by-Step Instructions for Injection".

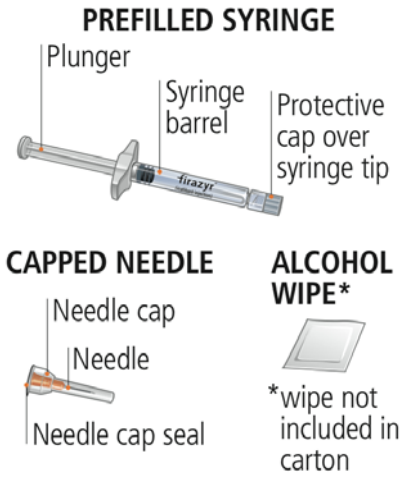
Usual adult dose:

- One injection (30 mg/3 mL) to be injected under the skin (subcutaneous) as directed by your doctor when you have symptoms of an HAE attack.
- If you have a laryngeal attack (obstruction of the upper airway), inject FIRAZYR and then go to the emergency room of the nearest hospital for medical help right away.
- If the symptoms continue or come back, you may repeat another injection (30 mg/3mL) after at least 6 hours from the first injection.

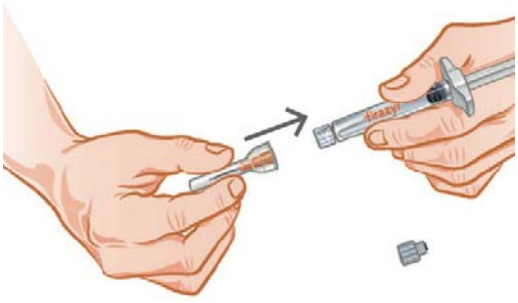
Do not use more than 3 injections in 24 hours. Talk with your doctor before using more than 8 doses per month.

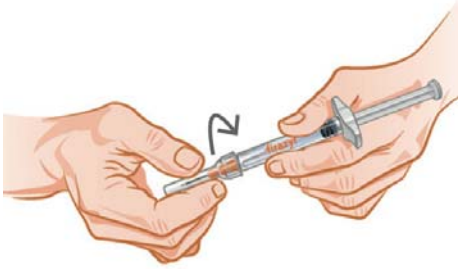
Step-by-Step Instructions for Injection:

1 - Getting started with FIRAZYR

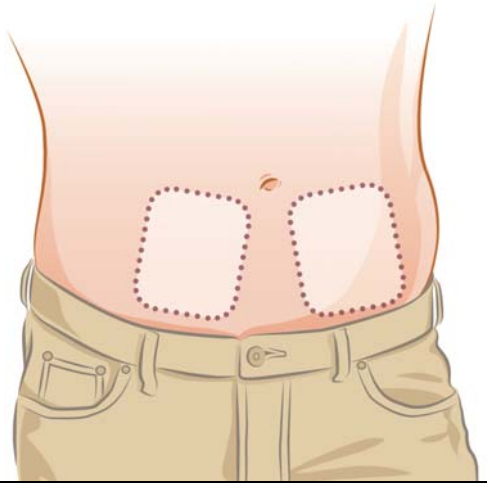
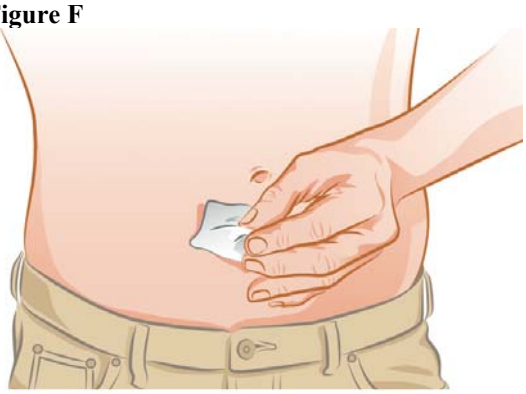
You will need the following supplies: • Your FIRAZYR blister pack, which includes 1 single-use, prefilled syringe and 1 needle • An alcohol wipe. **See Figure A** **Note:** The medicine inside your FIRAZYR prefilled syringe should be clear and colorless. Do not use your FIRAZYR prefilled syringe if the solution contains particles, is cloudy, or has an unusual color. If you believe that your FIRAZYR injection is not fit for use or is faulty in any way, please contact Shire at 1-888-867-7426. Remember to wash your hands with soap and water before handling any of the items needed for your injection, and always handle supplies carefully to avoid contamination.	**Figure A** 

2 - Preparing your dose of FIRAZYR

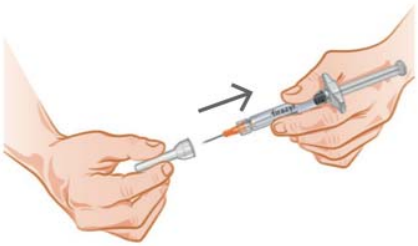
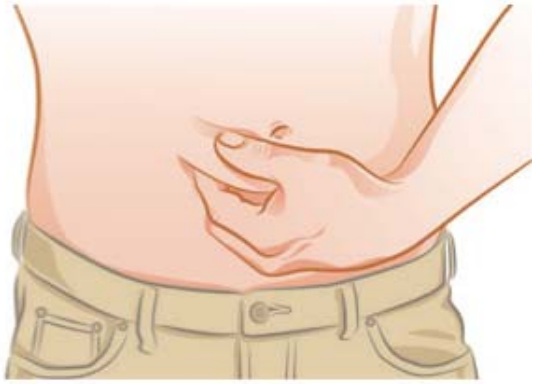
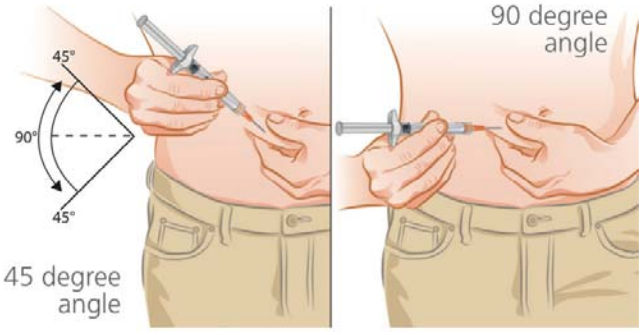
• Remove the prefilled syringe and needle from the blister pack.	
• Remove the seal from the needle cap (the needle should remain inside the protective needle cap until ready to use). **See Figure B**	**Figure B** 
• Hold the syringe firmly and remove the protective cap from the prefilled syringe. • Carefully attach the needle to the prefilled syringe containing the colorless FIRAZYR solution. **See Figure C**	**Figure C** 

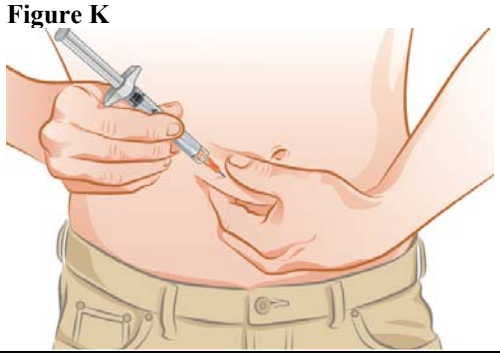
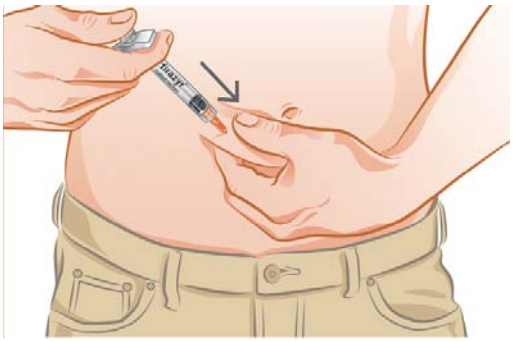
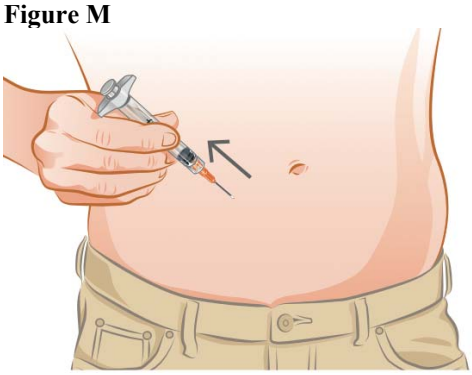
• Firmly screw the needle on the prefilled syringe. Be careful not to remove the needle from the needle cap. **See Figure D**	**Figure D** 

3 - Preparing the injection site

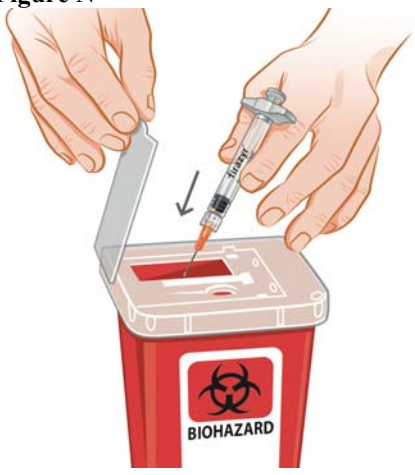
• Choose the injection site. The injection site should be a fold of skin on your stomach, about 5 to 10 centimeters (2 to 4 inches) below your belly button on either side. **See Figure E** The area you choose for injection should be at least 5 centimeters (2 inches) away from any scars. Do not choose an area that is bruised, swollen, or painful.	**Figure E** 
• Clean your FIRAZYR injection site with an alcohol wipe and allow it to dry. **See Figure F**	**Figure F** 

4 – Injecting FIRAZYR

• Remove the needle from the needle cap by holding the needle cap and carefully pulling the syringe. Do not pull up on the plunger. **See Figure G**	**Figure G** 
• Hold the FIRAZYR prefilled syringe in 1 hand, between your fingers and thumb. **See Figure H**	**Figure H** 
• Use your other hand to gently pinch the fold of skin you cleaned with the alcohol wipe between your thumb and fingers for your injection. **See Figure I**	**Figure I** 
• Hold the syringe between a 45 to 90 degree angle to your skin with the needle facing the fold of skin you are holding. **See Figure J**	**Figure J** 

• Hold the fold of skin. Bring the syringe to the skin and quickly insert the needle into the skin fold. **See Figure K**	**Figure K** 
• Push the plunger, at the top of the syringe, over at least 30 seconds until no FIRAZYR is in the syringe. **See Figure L**	**Figure L** 
• Release the skin fold and gently pull the needle out. **See Figure M**	**Figure M** 

5 - Disposing of your used FIRAZYR prefilled syringe

• Place the used FIRAZYR syringe, with the needle attached, in a sharps container (such as a biohazard container), a hard plastic container (such as a detergent bottle), or a metal container (such as an empty coffee can). Seal the container and throw it away the right way. There may be provincial and local laws about the right way to throw away used syringes and needles. Ask your healthcare provider or pharmacist how to throw away used syringes and needles. **See Figure N**	**Figure N** 

Overdose:

In case of drug overdose, contact a healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- burning, redness, swelling, pain, itching, or warmth at the injection site
- abdominal pain or distension
- diarrhea
- fever
- upper respiratory tract infection
- inflammation of the sinuses
- urinary tract infection
- increased liver enzymes called transaminases (ALT, AST)
- dizziness
- headache
- worsening or recurrence of HAE
- rash
- nausea
- nasal congestion

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Uncommon	Irregular heartbeat			X
Unknown	heart and non-heart related chest pain			X
	acute heart attack			X
	increased liver enzymes (ALT, AST)		X	

Tell your healthcare professional if you have any side effect that bothers you or that does not go away.

This is not a complete list of side effects. For any unexpected effects while taking FIRAZYR, contact your doctor or pharmacist.

HOW TO STORE IT

Store at: 2-25° C Do not freeze.
Store FIRAZYR in the original carton until you are ready to use it.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701E
  Ottawa, Ontario
  K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your healthcare professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about FIRAZYR:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website http://hc-sc.gc.ca; www.shirecanada.com, or by calling Paladin Labs Inc. at 1-888-867-7426.

This leaflet was prepared by Shire Orphan Therapies, LLC
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