

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr **FIRAZYR**®*

icatibant injection

Solution, Single-Use Prefilled Syringe

For Subcutaneous use

30 mg / 3 mL (10 mg / mL) of icatibant (as icatibant acetate)

Drugs used in hereditary angioedema

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Date of Authorization:
OCT 24, 2024

Submission Control Number: 287307

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RECENT MAJOR LABEL CHANGES

None at time of most recent authorization

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Sections or subsections that are not applicable at the time of the most recent authorized product monograph are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

FIRAZYR (icatibant injection) is indicated for:

- the treatment of acute attacks of hereditary angioedema (HAE) in adults, adolescents and children aged 2 years and older with C1-esterase inhibitor deficiency.

FIRAZYR is supplied through a controlled distribution program that is accessed by patients and pharmacies. Patients or a caregiver should be trained in subcutaneous injection techniques under the guidance of a healthcare professional before they can administer FIRAZYR (see 4.4 Administration).

1.1 Pediatrics

≥ 2 years to <18 years of age and weighing ≥12 kg: Based on the data submitted and reviewed by Health Canada, the safety and efficacy of FIRAZYR in pediatric patients aged 2 years and older who weigh ≥12 kg have been established. Therefore, Health Canada has authorized an indication for pediatric use.

< 2 years of age and in patients weighing < 12 kg: Studies in children aged less than 2 years or children weighing less than 12 kg have not been performed. No dosage regimen can be recommended in children aged less than two years or weighing less than 12 kg as the safety and efficacy have not been established (see 7.1.3 [Pediatrics](#)).

1.2 Geriatrics

Geriatrics (≥65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population demonstrated that the total exposure to icatibant was higher than in young adults (see 10.3 [Pharmacokinetics](#)).

2 CONTRAINDICATIONS

FIRAZYR is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

Takeda's OnePath Patient Support Program

FIRAZYR is supplied through a controlled distribution program that is accessed by patients and pharmacies. Patients should be enrolled in the OnePath Patient Support Program to receive FIRAZYR prefilled syringes and patient self-administration kits. Physicians and dispensers should encourage their patients to register in the OnePath Patient Support Program to obtain FIRAZYR and additional training and educational materials.

4.1 Dosing Considerations

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.

4.2 Recommended Dose and Dosage Adjustment

Adults: The recommended dose of FIRAZYR is 30 mg. 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.

Pediatrics (aged 2 to 17 years): The recommended dose of FIRAZYR based on body weight is provided in Table 1 below.

Table 1 - Dosage Regimen for Pediatric Patients

Body Weight	Dose (Injection Volume)
12 kg to 25 kg	10 mg (1.0 mL)
26 kg to 40 kg	15 mg (1.5 mL)
41 kg to 50 kg	20 mg (2.0 mL)
51 kg to 65 kg	25 mg (2.5 mL)
>65 kg	30 mg (3.0 mL)

In the clinical trial, not more than 1 injection of FIRAZYR per HAE attack was administered.

Pediatrics (< 2 years of age and in patients who weigh less than 12 kg): No dosage regimen can be recommended as the safety and efficacy have not been established (see 14 CLINICAL TRIALS).

Geriatrics (≥65 years of age): Patients 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 (see 10.3 [Pharmacokinetics](#)).

Hepatic Impairment: No dosage adjustment is required.

Renal Impairment: No dosage adjustment is required.

4.4 Administration

FIRAZYR is recommended to be initiated under the supervision of a physician experienced in the treatment of HAE.

FIRAZYR is supplied as a single-use prefilled syringe that delivers 3 mL of solution, equivalent to a 30 mg icatibant dose. The syringe and needle 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 discolouration prior to administration.

The drug solution should be clear and colourless. Do not administer if the product contains particulates or is discoloured.

Adult Patients

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

Adult 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 adult patients and caregivers directly through Takeda's OnePath Patient Support Program.

Pediatric Patients

Pediatrics (aged 2 years and above who weigh between ≥ 12 kg and ≤ 65 kg): attach the provided 25 gauge needle to the graduated syringe hub containing the required injection volume (dose) and screw on securely. Do not use a different needle. Disinfect the injection site and administer FIRAZYR by slow subcutaneous injection in the abdominal area over at least 30 seconds.

Pediatrics (adolescents weighing > 65 kg): attach the provided 25 gauge needle to the prefilled syringe hub and screw on securely. Do not use a different needle. Disinfect the injection site and administer FIRAZYR by slow subcutaneous injection in the abdominal area over at least 30 seconds.

FIRAZYR may be administered to children and adolescents (≥ 2 to < 18 years) by a healthcare professional. FIRAZYR may also be self-administered, if appropriate, or administered by a caregiver only after training in subcutaneous injection technique by a healthcare professional. Self-administration may require measurement of the correct dose of FIRAZYR. Ensure patients have received adequate training in the preparation of the empty graduated syringe, measurement of the correct dose of FIRAZYR, and transfer of the dose to the graduated syringe. Self-administration training is also available directly through Takeda's OnePath Patient Support Program.

The required injection volume in mL (derived from Table 1) from the prefilled syringe should be transferred into an empty, 3 mL graduated syringe for subcutaneous injection. Supplies required for extracting the appropriate dose from the prefilled syringe for pediatric patients (3 mL graduated syringes and connectors), as well as alcohol wipes may be obtained through Takeda's OnePath Patient Support Program.

4.5 Missed Dose

Not applicable.

5 OVERDOSE

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, flushing or hypotension in healthy subjects. No therapeutic intervention was necessary.

There are no specific data in pediatric patients related to overdose.

For management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 - Dosage Forms, Strengths and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous	Solution / 30 mg / 3 mL (10 mg/mL) icatibant as icatibant acetate	acetic acid glacial, sodium chloride, sodium hydroxide and water for injection

Description

FIRAZYR is supplied as a sterile solution for subcutaneous injection in a single-use prefilled syringe. The solution is clear and colourless.

Each prefilled 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 prefilled 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.

The carton includes one prefilled syringe with one needle.

A patient self-administration kit, containing a travel case, needle protection devices and alcohol wipes can be obtained through Takeda's OnePath Patient Support Program. Pediatric patients must obtain a separate self-administration kit through Takeda's OnePath Patient Support Program, which contains a travel case, needle protection devices, connectors, graduated syringes, and alcohol wipes.

7 WARNINGS AND PRECAUTIONS

General

FIRAZYR is recommended to be initiated under the supervision of a physician experienced in the treatment of HAE. 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 self-administration of FIRAZYR should be performed under the guidance of a healthcare professional. Administration of FIRAZYR to children and adolescents should be performed by a healthcare professional, caregiver, or through self-administration, if appropriate (see 4.4 [ADMINISTRATION](#)).

Patients with laryngeal symptoms or any swelling causing breathing difficulties should seek medical attention immediately after administration of FIRAZYR (see 4.1 Dosing Considerations). Asphyxia may occur more rapidly in children than adults due to smaller airway passages. The safety and efficacy of FIRAZYR for the treatment of laryngeal symptoms is based on limited data in pediatric patients (see 14 CLINICAL TRIALS).

Cardiovascular

Ischemic Heart Disease

FIRAZYR has been shown to aggravate induced cardiac ischemia in several animal models by antagonising the cardioprotective effects of bradykinin (see 10.2 [Pharmacodynamics](#)). Use of FIRAZYR 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.

Cerebrovascular Accident

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

Driving and Operating Machinery

While taking FIRAZYR, patients should be cautioned not to drive, operate dangerous machinery or engage in activities that require alertness or physical coordination. The following symptoms have been reported following the use of FIRAZYR and may occur as a result of an attack of HAE: Fatigue; lethargy; tiredness; somnolence; and dizziness.

Hepatic/Biliary/Pancreatic

Hepatic impairment: Data from subjects with a wide range of hepatic insufficiency suggest that FIRAZYR exposure is not influenced by hepatic impairment. No dosage adjustment is required in patients with hepatic impairment (See 10.3 [Pharmacokinetics](#)).

Monitoring and Laboratory Tests

Monitoring reproductive hormone concentrations should be considered in children and adolescents receiving frequent FIRAZYR treatment (see 16 NON-CLINICAL TOXICOLOGY).

Renal

Renal impairment: Limited data from subjects with renal insufficiency suggest that FIRAZYR exposure is not influenced by renal impairment. No dosage adjustment is required in patients with renal impairment (See 10.3 [Pharmacokinetics](#)).

Reproductive Health

- **Fertility**

The long-term effects of frequent treatment with FIRAZYR in children and adolescents are unknown. Nonclinical studies administering FIRAZYR at a high-frequency of high doses in rats and dogs, in which FIRAZYR was administered on a daily basis for 7 and 13 weeks, respectively, demonstrated treatment-related, reversible impairment of sexual maturation and degeneration in sexual organs (See 16 NON-CLINICAL TOXICOLOGY).

7.1 Special Populations

7.1.1 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 FIRAZYR had effects in late stage pregnancy where FIRAZYR 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 16 NON-CLINICAL TOXICOLOGY).

7.1.2 Breastfeeding

Animal studies showed that FIRAZYR is excreted in the milk of lactating rats at concentrations similar to those in maternal blood. It is unknown whether FIRAZYR is excreted in human breast milk. Many drugs are excreted in human milk, therefore caution should be exercised.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): FIRAZYR is indicated for use in adolescents and children aged 2 years and older. The safety and efficacy of FIRAZYR have not been established in children less than 2 years of age or weighing less than 12 kg, and limited information is available in children less than 6 years of age (See 14.1 Clinical Trials by Indication, 7 Reproductive Health, Fertility).

7.1.4 Geriatrics

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 10.3 Pharmacokinetics **Error! No bookmark name given.**).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adult Population

The majority of adult patients (97%) who were treated with subcutaneous 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 ($\geq 1\%$ to $<10\%$ of patients) were dizziness, headache, nausea, rash, erythema, pruritus, pyrexia, and increased transaminases (ALT and AST).

The overall incidence of serious adverse events (SAEs) in adult trials 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).

Pediatric Population

The majority of pediatric patients (90.6%) who were treated with subcutaneous FIRAZYR in the clinical trial developed reactions at the site of injection including erythema, swelling, burning sensation, warm sensation, cutaneous pain, and/or itching. These reactions were generally mild-to-moderate in severity, transient, and the majority resolved within 6 hours of FIRAZYR dosing. Other adverse reactions reported by patients treated with FIRAZYR ($\geq 1\%$ to $< 10\%$ of patients) and considered possibly related were dry mouth and fatigue. Each event occurred at a frequency of 3.1%.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

Adult Population

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

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

System Organ Class / Preferred Term	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		
Transaminases 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 3.

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 subcutaneously 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. No clinically significant changes in reproductive hormones were observed in adult subjects during clinical studies.

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.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

A total of 32 pediatric subjects (11 pre-pubertal and 21 pubertal/post-pubertal) with HAE were exposed to treatment with FIRAZYR during the open-label, nonrandomized, multicenter, single-arm clinical study, at a dose of 0.4 mg/kg based on body weight up to a maximum dose of 30 mg administered by a healthcare professional within 12 hours of the onset of symptoms. For pre-pubertal children, the mean age at study drug administration was 8.6 years, 100% of the subjects were Caucasian, and 54.5% of subjects were male. Of the 11 pre-pubertal children exposed to FIRAZYR, 2 were under the age of 6 years. For pubertal/post-pubertal pediatric patients, the mean age at study drug administration was 14.3 years, 95.2% of subjects were Caucasian, and 61.9% were male. Thirty-one patients received a single dose of FIRAZYR and 1 pubertal/post-pubertal patient received a single dose of FIRAZYR for each of two HAE attacks (in total, two doses).

The majority of pediatric patients (N=29 [90.6%]) treated with subcutaneous FIRAZYR experienced mild to moderate injection site reactions such as erythema, swelling, burning sensation, skin pain, and itching/pruritus. These reactions are consistent with reactions that have been reported in adults. Two pediatric patients experienced injection site reactions which were assessed as severe and which were completely resolved within 6 hours. Other adverse reactions reported and considered possibly related were dry mouth and fatigue. Each event occurred at a frequency of 3.1%.

No clinically significant changes in reproductive hormones were observed in pediatric subjects following a single FIRAZYR exposure in the 90-day clinical study period.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Liver enzyme tests

Transaminase levels (ALT, AST) were increased in 4% of adult patients treated with FIRAZYR (See Table 3).

8.5 Post-Market Adverse Reactions

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.
Hypersensitivity:	Urticaria
Product issues:	Drug ineffectiveness, device failure

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Formal drug-drug interaction studies have not been conducted with FIRAZYR. Pharmacokinetic drug interactions involving CYP450 are not expected (see 10.3 Pharmacokinetics, Metabolism). The treatment with FIRAZYR may interfere with the mode of action of angiotensin converting enzyme inhibitor (ACE-I) products.

9.3 Drug-Behaviour Interactions

The interaction of FIRAZYR with individual behavioural risks (e.g. cigarette smoking, cannabis use, and/or alcohol consumption) has not been studied.

9.4 Drug-Drug Interactions

Table 4 - Established or Potential Drug-Drug Interactions

FIRAZYR	Source of Evidence	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

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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.

10.2 Pharmacodynamics

Following bradykinin challenge, development of bradykinin-induced hypotension, vasodilation, and reflex tachycardia was prevented in healthy young adult 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 adult 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.

10.3 Pharmacokinetics

Table 5 - Summary of Icatibant's Pharmacokinetic Parameters in Healthy Adult Subjects Following Subcutaneous Administration

	C_{max}	$t_{1/2}$ (h)	$AUC_{0-\infty}$	CL	Vd
Single dose mean (30 mg)	974 ± 280 ng/mL	1.4 ± 0.3 hours	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 adult 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-∞}) 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.

Elimination

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

- Pediatrics:** The pharmacokinetics of icatibant were characterized in one study for pediatric HAE patients. Following subcutaneous administration, the time to maximum concentration was approximately 30 minutes and the terminal half-life was approximately 2 hours. There were no observed differences in the exposure to icatibant between patients first treated with icatibant during an HAE attack, and those first treated with icatibant in the absence of an attack. Population pharmacokinetic modeling using both adult and pediatric data showed that the exposure to icatibant in the pediatric HAE population following a single subcutaneous 0.4 mg/kg administration was lower than in adult HAE patients. Despite lower exposure, the 0.4 mg/kg subcutaneous dose of icatibant in pediatric patients was sufficient to produce a clinically meaningful treatment response (overall median time to minimal symptoms was 1.1 hours); in all patients, the HAE symptoms were either mild or absent within 6 hours of icatibant administration.

Following the 5 weight-band dosing regimen, the greatest exposure values are expected to be observed in the subjects in the lowest body weight category (12-25 kg) receiving the lowest dose (10 mg [1.0 mL]) of FIRAZYR.

- Geriatrics:** patients (>65 years of age) have been shown to have increased systemic exposure to icatibant.
- Hepatic Insufficiency:** Clinical pharmacokinetic studies demonstrate that for mild to moderate impairment of hepatic function, no dose adjustment is necessary. Icatibant clearance in subjects with a wide range of hepatic impairment (Child-Pugh score ≥ 7 and ≤ 15) was similar to that of healthy subjects.
- Renal Insufficiency:** Clinical pharmacokinetic studies demonstrate that for mild to moderate impairment of renal 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.
- Obesity:** The plasma clearance was higher in patients with increased body weight.

11 STORAGE, STABILITY AND DISPOSAL

Store at 2 to 25°C; do not freeze. Any unused product or waste materials should be disposed of in accordance with local requirements.

12 SPECIAL HANDLING INSTRUCTIONS

The solution should be clear and colourless and free from visible particles. Prefilled syringes are for single use only.

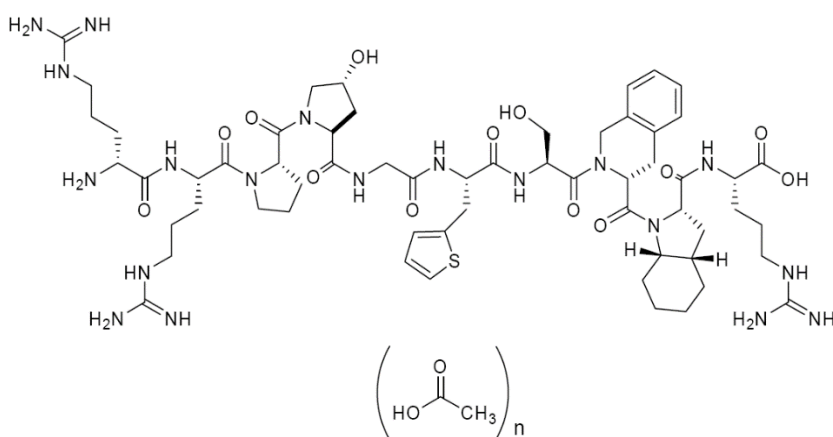
PART II: SCIENTIFIC INFORMATION**13 PHARMACEUTICAL INFORMATION****Drug Substance**

Non-proprietary name of the drug product(s): icatibant (as 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: C₅₉H₈₉N₁₉O₁₃S (net), 1304.55 g/mol (average, net)

Structure (for biologics)/Structural formula:



Physicochemical properties: a synthetic decapeptide with five non-proteinogenic amino acids.

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

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

HAE

Table 6 - Summary of patient demographics for clinical trials in HAE

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Age (Range)	Sex
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 30 mg/3 mL SC x 1 dose or placebo 3 mL SC x 1 dose.	93	36.8 years (18 to 83)	34 male; 59 female
	Open-label: Patients with severe laryngeal attack	FIRAZYR 30 mg/3 mL SC x 1 dose.	5	41.6 years (29 to 59)	3 male; 2 female
	Open-label extension: Patients with subsequent attacks	FIRAZYR 30 mg/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 30 mg/3 mL SC x 1 dose. or placebo 3 mL SC x 1 dose.	56	34.9 years (18 to 58)	19 male; 37 female
	Open-label: Patients with any laryngeal attack	FIRAZYR 30 mg/3 mL SC x 1 dose.	8	47.1 years (25 to 61)	3 male; 5 female
	Open-label extension: Patients with subsequent attacks	FIRAZYR 30 mg/3 mL SC for up to 3 doses at least 6 hours apart.	72	35.5 years (18 to 65)	23 male; 49 female

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Age (Range)	Sex
	Entire Study		84	36.6 years (18 to 65)	27 male; 57 female
Study 3 (FAST 2, JE049 #2102)	Randomized, double-blind, active-controlled: Patients with moderate to severe abdominal or cutaneous attacks	FIRAZYR 30 mg/3 mL 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 30 mg/3 mL SC x 1 dose.	3	35.0 years (27 to 48)	2 male; 1 female
	Open-label extension: Patients with subsequent attacks	FIRAZYR 30 mg/ 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 30 mg/3 mL SC x 1 dose.	104	41.6 years (18 to 76)	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
Study 5 (HGT-FIR-086)	Open-label Any cutaneous, abdominal, or laryngeal symptoms of an acute attack	FIRAZYR Single dose 0.4 mg/kg SC up to a maximal dose of 30 mg.*	32	12.3 years (3.4 to 17.4)	19 male 13 female

SC=subcutaneous; HCP=Healthcare professional

*One patient received 2 doses for two separate HAE attacks

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 1 was 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 subcutaneous 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 subcutaneous 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 subcutaneous 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 colour. Initial treatment of the attack in the double-blind phase consisted of 1 subcutaneous injection of FIRAZYR administered with 2 capsules of placebo (oral) or 1 subcutaneous 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 subcutaneous. 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 subcutaneous 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 7 below.

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

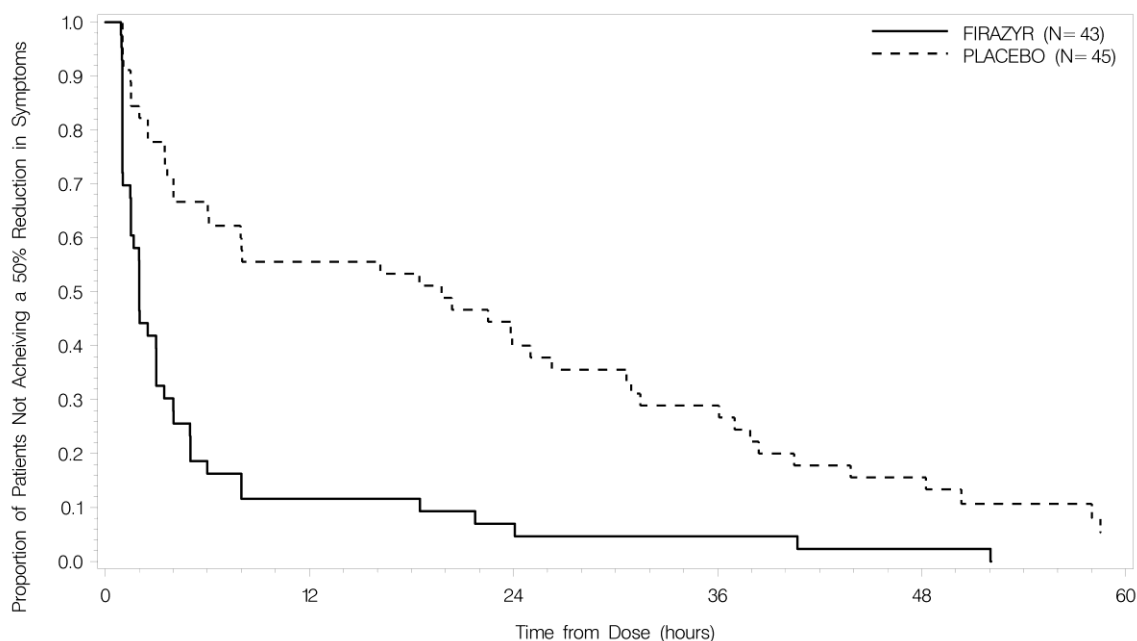


Table 7 - Results of studies 1, 2, and 3 in the non-laryngeal ITT population

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 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 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 ≥30 mm. For a pre-treatment VAS < 30 mm, 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 7 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 8 - 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 earliest of 3 consecutive non-missing measurements for which there was any reduction below (6/7) pre-treatment value – 16 for pretreatment VAS ≥ 30 mm. For a pre-treatment VAS < 30 mm, 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.

Pediatric Population

An open label, non-randomized single-arm study, Study 5, was performed with a total of 32 patients. All patients received at least one dose of icatibant (0.4 mg/kg body weight up to a maximum dose of 30 mg) and the majority of patients were followed-up for a minimum of 90 days following administration. Eleven patients were of pre-pubertal status (Tanner stage I) and 21 patients were either pubertal or post-pubertal (Tanner stages II to V).

The efficacy population consisted of 22 patients who had been treated with icatibant (11 pre-pubertal and 11 pubertal/post-pubertal) for a first HAE attack. Ten additional pubertal/post-pubertal subjects were treated with icatibant in the absence of an acute HAE attack. The safety population consisted of the 32 subjects overall.

The primary efficacy endpoint was the time to onset of symptom relief (TOSR) measured using a composite investigator-reported symptom score. Time to symptom relief was defined as the duration of time (in hours) taken for improvement of symptoms to occur by a magnitude of 20%. Table 8 shows the efficacy results for Study 5.

Table 9 - Efficacy results for Study 5

Parameter	Pre-pubertal (n=11)	Pubertal/post-pubertal (n=11)	Overall (n=22)
Median time to onset of symptom relief (hours)	1.0	1.0	1.0
95% CI for median time (hours)	1.0, 2.0	1.0, 2.0	1.0, 1.1

CI = confidence interval

At 1 and 2 hours post treatment, approximately 50% and 90% of patients experienced onset of symptom relief, respectively.

Overall, the median time to minimal symptoms (earliest time post treatment when all symptoms were either mild or absent) was 1.1 hours (95% confidence interval, 1.0-2.0 hours).

The safety and efficacy of FIRAZYR for treatment of acute laryngeal attacks have not been established in pediatric patients. Of the 23 on-study HAE attacks included in the pediatric clinical trial, one was a laryngeal attack. This attack was the second treated attack for one adolescent subject. The subject received FIRAZYR 3 hours and 40 minutes following the onset of laryngeal symptoms, which included mild dysphagia and mild erythema. The time to onset of symptom relief and the time to initial symptom relief as assessed by the investigator were 4 hours for this attack and the time to onset of pain relief as assessed by the subject was 4 hours. No rescue medications were required.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

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 were 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 subcutaneous 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).

Genotoxicity

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

Reproductive and Developmental Toxicology

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

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr **FIRAZYR**[®]

Icatibant injection

This Patient Medication Information is written for the person who will be taking **FIRAZYR**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have questions about the condition this medication is for or want more information about **FIRAZYR**, talk to a healthcare professional.

Takeda's OnePath Patient Support Program has been set up to give training on how to use FIRAZYR. It will give you information and answer any questions you may have. FIRAZYR and supplies needed to inject it are provided through this Program. Speak to your healthcare professional to enroll.

What is **FIRAZYR** used for?

FIRAZYR is used to treat acute attacks of hereditary angioedema (HAE). It is used in adults and children aged 2 years and older, with a deficiency of a protein called C1-esterase inhibitor.

How does **FIRAZYR** work?

In HAE, levels of a substance in your bloodstream called bradykinin are increased. This can cause swelling, pain, nausea, and diarrhea. **FIRAZYR** blocks the activity of bradykinin. This stops the symptoms of an HAE attack from getting worse.

What are the ingredients in **FIRAZYR**?

Medicinal ingredients: icatibant (as icatibant acetate)

Non-medicinal ingredients: acetic acid glacial, sodium chloride, sodium hydroxide and water for injection

FIRAZYR comes in the following dosage forms:

Solution for injection, 30 mg / 3 mL (10 mg / mL)

Do not use **FIRAZYR** if:

- you are allergic to icatibant acetate or to any ingredient in this medicine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take **FIRAZYR. Talk about any health conditions or problems you may have, including 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 or plan to breastfeed.

Other warnings you should know about:

Only a doctor who has experience treating patients with HAE is recommended to treat you with FIRAZYR.

Caregivers/Self-administration:

- Your first injection of FIRAZYR should be given under the guidance of a healthcare professional. Your healthcare professional will tell you when it is safe to go home.
- You or your caregiver may inject FIRAZYR only after receiving training on how to use it. A healthcare professional will teach you how to use it.
- Self-injection for children is not recommended. FIRAZYR should only be given to children by a healthcare professional or caregiver.
- Adolescents may only self-inject if their doctor and caregiver agree that it is appropriate for them to do so.

Laryngeal HAE attacks:

- A laryngeal HAE attack, or an attack of the throat, can become life threatening. This is because increased swelling of the throat can create a blockage of the upper airway. This in turn makes breathing difficult.
- If you have a laryngeal HAE attack:
 - inject FIRAZYR, and
 - go to the nearest hospital emergency room for medical help right away.
- A blockage of the airway may occur faster in children and adolescents than in adults. This is because the airway passage is smaller in these patients.

Adolescents and Children:

- FIRAZYR is not recommended for use in children under 2 years of age or those who weigh less than 12 kg
- There is limited experience with the use of FIRAZYR in the treatment of:
 - children under 6 years of age
 - laryngeal HAE attacks in adolescents and children

Effects on Reproductive Organs in Adolescents and Children aged 2 years and above:

- The effects of long-term FIRAZYR use are not known.
- Early studies have shown that when FIRAZYR is used often, it may cause damage to the reproductive system or may affect how it develops.
- Your healthcare professional may do blood tests to check how your or your child's reproductive organs are working.

Pregnancy and Breastfeeding:

- It is not known if FIRAZYR will harm your unborn baby. If you are pregnant or planning to become pregnant, speak to your healthcare professional before using FIRAZYR. You and your healthcare professional will decide if FIRAZYR is right for you.
- It is not known if FIRAZYR passes into breast milk. If you are breast-feeding or planning to breast-feed, speak to your healthcare professional before using FIRAZYR about the best way to feed your baby.

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.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with FIRAZYR:

- Angiotensin converting enzyme (ACE) inhibitor (used to lower blood pressure).

How to take FIRAZYR:

- You may inject FIRAZYR only after receiving training on how to use it.
- Always use FIRAZYR exactly as your healthcare professional has shown you.
- Be sure to use each FIRAZYR prefilled syringe only once, even if there is still medicine in it.
- FIRAZYR is given as a single injection under the skin on the stomach. This is called a subcutaneous injection.
- In adults and adolescents who weigh more than 65 kg:
 - The FIRAZYR prefilled syringe will be used to give the injection.
- In adolescents who weigh **65 kg or less** and children aged 2 years and above:
 - Some FIRAZYR will need to be transferred from the prefilled syringe into an empty graduated syringe. This graduated syringe will then be used to inject FIRAZYR.

Read and follow the below STEP-BY-STEP INSTRUCTIONS FOR INJECTION. It will take you through the process to give a FIRAZYR injection.

The solution should be clear and colourless and free from visible particles. Do not use this medication if it looks cloudy or is leaking. Prefilled syringes are for single use only.

Usual dose:**All Patients:**

- Take FIRAZYR as soon as you have symptoms of an HAE attack. Symptoms can include swelling, pain, nausea, and diarrhea.
- **If you have a laryngeal HAE attack, inject FIRAZYR and then go to the nearest hospital emergency room for medical help right away.**

Adults:

- The recommended dose is 3 mL. Use the full contents of the FIRAZYR prefilled syringe.
- If the symptoms continue, worsen, or come back, and it has been at least 6 hours from the first injection: give another injection.
- **Do not use more than 3 injections in 24 hours. Talk with your healthcare professional before using more than 8 doses per month.**

Adolescents (weighing more than 65 kg):

- The recommended dose is 3 mL. Use the full contents of the FIRAZYR prefilled syringe.
- **If the symptoms continue, worsen, or come back, seek immediate medical advice. Do not use more than 1 injection for a single HAE attack.**

Adolescents (weighing 65 kg or less) and Children (aged 2 and above):

- The recommended dose is between 1 mL to 2.5 mL. The dose is based on body weight.
- You will need to use only some of the FIRAZYR prefilled syringe.
- See the below STEP-BY-STEP INSTRUCTIONS FOR INJECTION for the dose to inject. If you are not sure, speak to your healthcare professional.
- The dose may change from one injection to the next with changes in body weight.
- **If the symptoms continue, worsen, or come back seek immediate medical advice. Do not use more than 1 injection for a single HAE attack.**

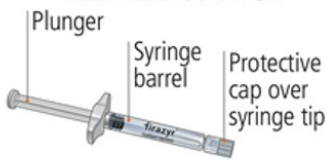
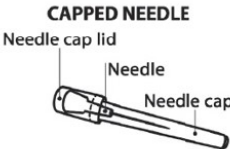

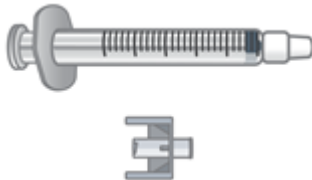
STEP-BY-STEP INSTRUCTIONS FOR INJECTION:

This section contains information on how to give an injection of FIRAZYR.

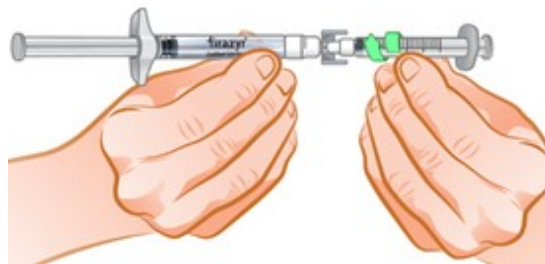
Read these instructions before using FIRAZYR and each time you get a repeat prescription. There may be new information.

These instructions are not meant to take the place of training by a healthcare professional. A healthcare professional will teach you and your caregiver how to give FIRAZYR. Ask your healthcare professional any questions you may have. **Do NOT attempt to inject FIRAZYR until you are sure how to and your doctor has determined that it is appropriate for you to do so.**

Takeda's OnePath Patient Support Program has been set up to provide guidance and additional training on how to use FIRAZYR. It will give you information and answer any questions you may have. FIRAZYR and supplies needed to give it are provided through this Program. Information including training can be obtained through the Program by calling Takeda at 1-800-268-2772.

Step 1 – Gather supplies	ALL PATIENTS Adults, Adolescents and Children (Aged 2 years and above)
Collect the following listed items to prepare and give the injection:	
Items provided to you with your FIRAZYR prescription:	
<p>1) Your FIRAZYR carton, which includes:</p> <ul style="list-style-type: none"> • One single-use prefilled syringe (containing 3 mL of FIRAZYR solution). • One capped needle. 	<p>PREFILLED SYRINGE</p>  <p>CAPPED NEEDLE</p> 
<p>2) The administration supplies, which include(s):</p> <ul style="list-style-type: none"> • One alcohol wipe. 	<p>ALCOHOL WIPE</p> 
For Adolescents (weighing 65 kg or less) and Children (Aged 2 years and above),	
<ul style="list-style-type: none"> • The following supplies are needed to measure out and transfer the dose: <ul style="list-style-type: none"> ▪ One 3 mL graduated syringe. ▪ One connector. 	
Not provided with FIRAZYR:	
<p>3) A sharps disposal container.</p> <ul style="list-style-type: none"> • If you do not have a sharps disposal container, you may use a household container that is: <ul style="list-style-type: none"> ▪ Made of heavy-duty plastic or metal. An empty detergent bottle or coffee can may be used. ▪ Properly labelled. Using a marker, write “BIOHAZARD” on the container. 	

Step 2 – Getting started with FIRAZYR	ALL PATIENTS Adults, Adolescents and Children (Aged 2 years and above)
<ul style="list-style-type: none"> • Find a clean surface to work and place your supplies. • Wash your hands with soap and water. Dry your hands well. • Remove the supplies from Step 1 from their packaging. Place them on the clean work surface. • Visually check the FIRAZYR prefilled syringe to make sure: <ul style="list-style-type: none"> ▪ the medicine is clear, colourless and does not contain particles. ▪ the prefilled syringe is not damaged. ▪ the expiry date has not passed. The expiry date can be found on the prefilled syringe and the outer carton label. <p>If any of the above are not met:</p> <ul style="list-style-type: none"> • Do NOT use the syringe, and • go to the nearest hospital emergency room to seek medical help right away. <ul style="list-style-type: none"> • Hold the FIRAZYR prefilled syringe firmly. • Remove the protective cap from the end of the FIRAZYR prefilled syringe. • Put down the FIRAZYR prefilled syringe on the clean work surface. <div style="border: 1px solid black; padding: 10px; margin: 10px 0;"> <p>Adults and Adolescents (weighing more than 65 kg):</p> <ul style="list-style-type: none"> ○ Skip Step 3, and ○ Proceed to Step 4. <p>Adolescents (weighing 65 kg or less) and Children (Aged 2 years and above):</p> <ul style="list-style-type: none"> ○ Proceed to Step 3. </div>	
Step 3 – Preparing the Graduated Syringe – Measuring out and transferring the dose from the FIRAZYR prefilled syringe	ADOLESCENTS (weighing 65 kg or less) and CHILDREN (Aged 2 years and above)
<p>A) Preparing the Empty Graduated Syringe and Connector</p> <ul style="list-style-type: none"> • Remove the caps on each end of the connector. <p>Avoid touching the ends of the connector and syringe tips to prevent contamination.</p> <ul style="list-style-type: none"> • Screw the connector onto the FIRAZYR prefilled syringe. • Attach the graduated syringe to the other end of the connector. Make sure that both connections fit securely. 	



B) Transferring FIRAZYR to the Empty Graduated Syringe

- Use the table below to determine how much FIRAZYR you will need to measure out and transfer.
If you are not sure of how much solution to draw up, ask your healthcare professional.

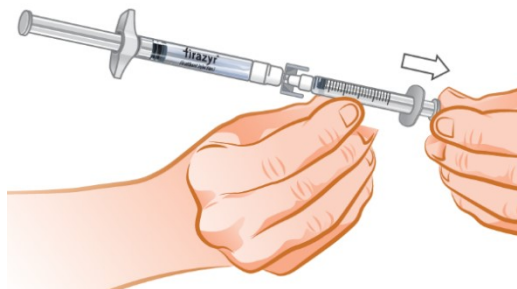
Dosing for Adolescents and Children:

Body Weight	Volume (Dose) to Measure Out and Transfer
12 kg to 25 kg	1.0 mL
26 kg to 40 kg	1.5 mL
41 kg to 50 kg	2.0 mL
51 kg to 65 kg	2.5 mL

- Push the plunger of the FIRAZYR prefilled syringe slowly. This will start the transfer of FIRAZYR.



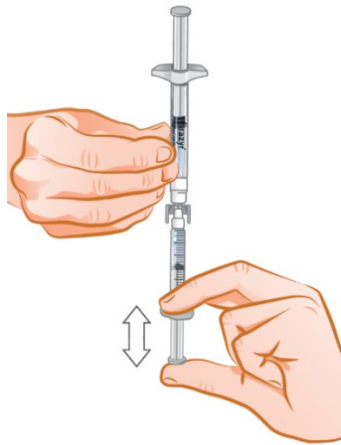
- If the FIRAZYR solution does not begin to transfer to the graduated syringe, pull slightly on the plunger of the graduated syringe. Do this until the FIRAZYR solution starts to flow into the graduated syringe.



- Continue to push on the plunger of the prefilled syringe. Do this until the required injection volume (dose) is transferred to the graduated syringe. Use the markings on the graduated syringe to measure the dose.

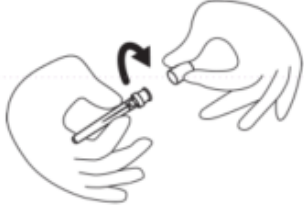
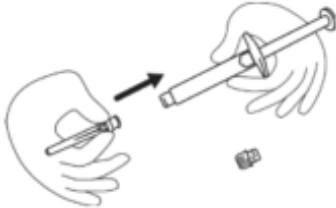
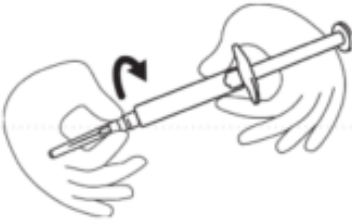
C) If there is Air in the Graduated Syringe:

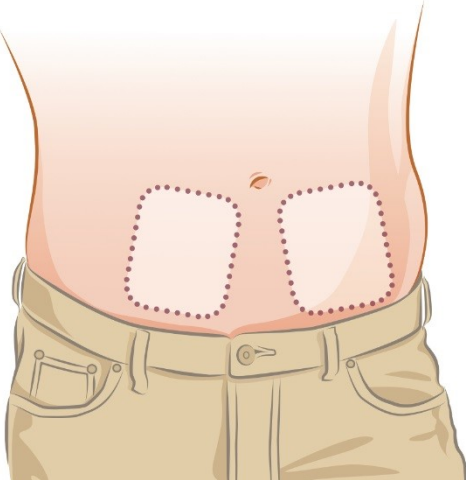

- Turn the connected syringes so that the prefilled syringe is on top.
- Push the plunger of the graduated syringe to transfer any air back into the prefilled syringe.
- Pull gently on the plunger of the graduated syringe. Do this until the required injection volume is transferred to the graduated syringe. Use the marking on the graduated syringe to measure the dose.
- You may need to repeat these actions several times.



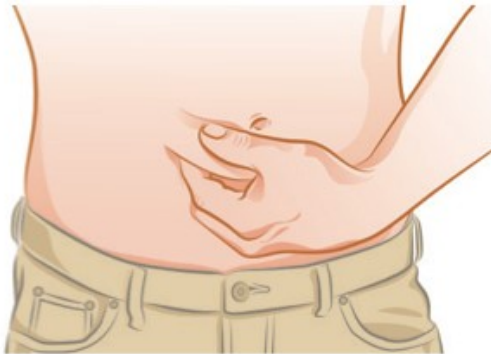


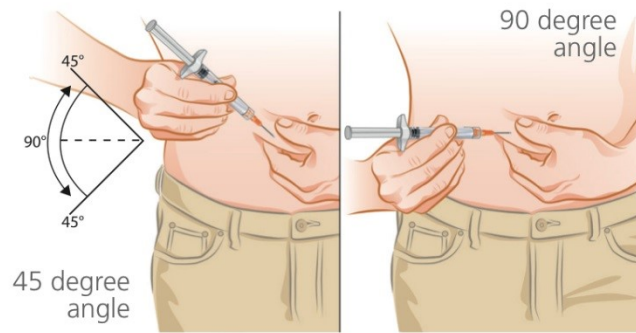
D) Disconnect the Graduated Syringe:

- Remove the FIRAZYR prefilled syringe and connector from the graduated syringe.
- Put down the graduated syringe on the clean work surface.
- Discard the FIRAZYR prefilled syringe and connector into a sharps disposal container.
Be sure to use each FIRAZYR prefilled syringe only once. Re-use may lead to infection or other illness/injury.

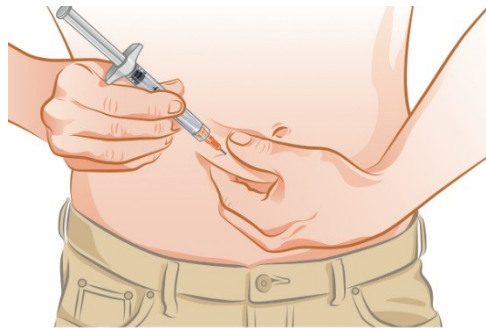
Step 4 – Preparing the syringe and needle for injection	ALL PATIENTS Adults, Adolescents and Children (Aged 2 years and above)
<ul style="list-style-type: none">• Remove the needle cap from the blister tray.• Twist the lid of the needle cap to break the seal.• Keep the needle inside the protective needle cap until ready to use.  <ul style="list-style-type: none">• Grip the syringe firmly.<ul style="list-style-type: none">▪ For adults and adolescents weighing more than 65 kg: The syringe is the FIRAZYR prefilled syringe.▪ For adolescents weighing less than 65 kg and children: The syringe is the graduated syringe.• Carefully attach the needle to the prefilled syringe.  <ul style="list-style-type: none">• Firmly screw the needle on the syringe containing the FIRAZYR dose. Be careful not to remove the needle from the needle cap. 	

Step 5 – Preparing the injection site	ALL PATIENTS Adults, Adolescents and Children (Aged 2 years and above)
<ul style="list-style-type: none">• Choose the injection site. The injection site should be a fold of skin on the stomach, about 5 to 10 centimeters (2 to 4 inches) below the belly button on either side.• 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.  <ul style="list-style-type: none">• Clean the FIRAZYR injection site with an alcohol wipe and allow it to dry. 	

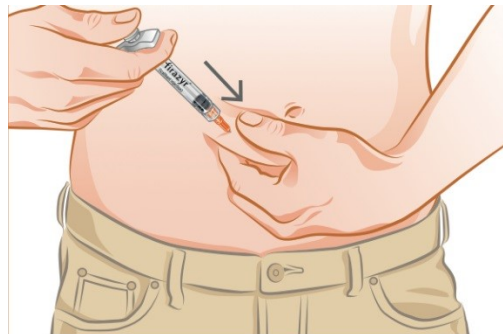
Step 6 – Injecting FIRAZYR	ALL PATIENTS Adults, Adolescents and Children (Aged 2 years and above)
<ul style="list-style-type: none"><li data-bbox="253 359 1385 426">• Remove the needle from the needle cap by holding the needle cap and carefully pulling the syringe. Do NOT pull up on the plunger.  <ul style="list-style-type: none"><li data-bbox="253 764 1052 795">• Hold the syringe in one hand, between your fingers and thumb.  <ul style="list-style-type: none"><li data-bbox="253 1144 1323 1211">• 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.  <ul style="list-style-type: none"><li data-bbox="253 1730 1393 1797">• Hold the syringe between a 45 to 90 degree angle to the skin with the needle facing the fold of skin you are holding.	



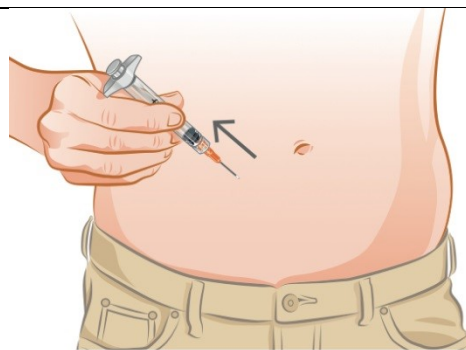
- Hold the fold of skin. Bring the syringe to the skin and quickly insert the needle into the skin fold.



- Slowly push the plunger at the top of the syringe over at least 30 seconds. Continue to push the plunger until no FIRAZYR is left in the syringe.



- Release the skin fold and gently pull the needle out.

**Step 7 – Disposing of your used syringe.****ALL PATIENTS**

**Adults, Adolescents and
Children (Aged 2 years and above)**

- Discard the used syringe, with the needle attached, into a sharps disposal container. Do NOT throw away used syringes in your household waste.
- **Always keep the sharps container out of the reach and sight of children.**
- When your sharps container is almost full, you will need to follow your local guidelines for the right way to throw away your sharps container. Ask your healthcare professional or pharmacist how to do this if you are unsure.
- Do NOT throw away any used sharps disposal container in your household waste. Do NOT recycle your used sharps container.

**Overdose:**

If you think you, or a person you are caring for, have taken too much FIRAZYR, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

Not applicable.

What are possible side effects from using FIRAZYR?

These are not all the possible side effects you may have when taking FIRAZYR. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- burning, redness, swelling, pain, itching, or warmth at the injection site
- abdominal pain or distension
- diarrhea
- nausea
- fever
- upper respiratory tract infection (common cold)
- inflammation of the sinuses
- nasal congestion
- dizziness
- headache
- worsening or recurrence of HAE
- rash
- hives
- dry mouth
- fatigue

FIRAZYR may affect certain liver enzyme levels in your blood. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious Side Effects and What To Do About Them

Frequency/Side Effect/Symptom	Talk to Your Healthcare Professional		Stop Taking the Drug and Get Immediate Medical Help
	Only if Severe	In All Cases	
UNCOMMON			
Arrhythmia (abnormal heart rhythms): rapid, slow or irregular heartbeat			X
Urinary Tract Infection (UTI) (infection in urinary system including kidneys, ureters, bladder and urethra): Pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine		X	
UNKNOWN			
Heart and non-heart related chest pain			X
Myocardial infarction (heart attack): pressure or squeezing pain between the shoulder blades, in			X

Frequency/Side Effect/Symptom	Talk to Your Healthcare Professional		Stop Taking the Drug and Get Immediate Medical Help
	Only if Severe	In All Cases	
the chest, jaw, left arm or upper abdomen, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint and possible irregular heartbeat.			
Increased levels of liver enzymes (ALT, AST) in the blood: dark urine, fatigue, loss of appetite, yellowing of the skin or eyes		X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at 2 to 25°C. Do not freeze.
- Store FIRAZYR in the original carton until you are ready to use it.
- Keep out of reach and sight of children.

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 Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website (<https://www.takeda.com/en-ca/what-we->

do/our-medicines), or by calling 1-800-268-2772.

- For information about Takeda's OnePath Patient Support Program, contact Takeda at 1-800-268-2772.

This leaflet was prepared by Takeda Canada Inc.

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Last revised: OCT 24, 2024

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