PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]Teva-Icatibant

icatibant injection

Solution, 30 mg / 3 mL (10 mg / mL) as icatibant acetate
Single-Use Prefilled Syringe, Subcutaneous

Drugs used in hereditary angioedema ATC Code: B06AC02

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[Pr]Teva-Icatibant

icatibant injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Subcutaneous	Solution / 30 mg / 3 mL (10 mg/mL) as icatibant acetate	Acetic acid glacial, sodium chloride, sodium hydroxide, and water for injection

INDICATIONS AND CLINICAL USE

Teva-Icatibant (icatibant acetate) 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.

Teva-Icatibant 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 Teva-Icatibant (see **DOSAGE AND ADMINISTRATION**).

Geriatrics (> 65 years of age):
Limited information is available regarding the use of icatibant injection in patients older than 65 years of age (see **WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Pediatrics (<18 years of age):
Teva-Icatibant is indicated for use in adolescents and children aged 2 years and older. Studies in children aged less than 2 years or 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.

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

Teva-Icatibant 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 Teva-Icatibant. The first self-administration of Teva-Icatibant should be performed under the guidance of a healthcare professional. Administration of Teva-Icatibant to children and adolescents should be performed by a healthcare professional, caregiver, or through self-administration, if appropriate (see **DOSAGE AND ADMINISTRATION**).

Patients with laryngeal symptoms or any swelling causing breathing difficulties should seek medical attention immediately after administration of Teva-Icatibant (see **DOSAGE AND ADMINISTRATION**). Asphyxia may occur more rapidly in children than adults due to smaller airway passages. The safety and efficacy of icatibant injection for the treatment of laryngeal symptoms is based on limited data in pediatric patients (see **CLINICAL TRIALS**).

Cardiovascular

Ischemic Heart Disease

Icatibant injection has been shown to aggravate induced cardiac ischemia in several animal models by antagonising the cardioprotective effects of bradykinin (see **DETAILED PHARMACOLOGY**). Use of Teva-Icatibant 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 Teva-Icatibant 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 icatibant injection in pregnant women have been conducted. Teva-Icatibant should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal studies showed that icatibant injection had effects in late stage pregnancy where icatibant injection 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 acetate is excreted in the milk of lactating rats at concentrations similar to those in maternal blood (see **DETAILED PHARMACOLOGY**). It is unknown whether Teva-Icatibant is excreted in human breast milk. Many drugs are excreted in human milk, therefore caution should be exercised.

Pediatrics (< 18 years of age)
Teva-Icatibant is indicated for use in adolescents and children aged 2 years and older. The safety and efficacy of icatibant injection 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 **CLINICAL TRIALS**, **Study Results**, **Pediatric Population**).

Growth and Development Effects in Pediatric Patients
The long-term effects of frequent treatment with icatibant injection in children and adolescents are unknown. Nonclinical studies administering icatibant injection at a high-frequency of high doses in rats and dogs, in which icatibant injection 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.

Monitoring reproductive hormone concentrations should be considered in children and adolescents receiving frequent Teva-Icatibant treatment (see **TOXICOLOGY**).

Geriatrics (> 65 years of age)
Limited information is available for Teva-Icatibant 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 injection 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 injection exposure is not influenced by renal impairment. No dosage adjustment is required in patients with renal impairment.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adult Population
The majority of adult patients (97%) who were treated with subcutaneous icatibant injection 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 icatibant injection dosing. Other adverse reactions reported by patients treated with icatibant injection (≥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 icatibant injection 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 icatibant injection. 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 icatibant injection-treated attacks for patients. Sixteen patients experienced a total of 22 SAEs that occurred within 14 days of icatibant injection 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 icatibant injection treatment (events of arrhythmia and noncardiac chest pain).

Pediatric Population
The majority of pediatric patients (90.6%) who were treated with subcutaneous icatibant injection 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 icatibant injection dosing. Other adverse reactions reported by patients treated with icatibant injection (≥1% to <10% of patients) and considered possibly related were dry mouth and fatigue. Each event occurred at a frequency of 3.1%.

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.

Adult Population

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

The safety of icatibant injection was evaluated in three controlled Phase III trials that included 223 patients who received subcutaneous injection of icatibant acetate 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 icatibant injection 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 icatibant injection-treated patients (2 or more patients), and at a higher frequency with icatibant injection 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 icatibant injection treatment were judged to be mild or moderate in severity.

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

	Icatibant Injection (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 icatibant injection 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 icatibant 30 mg and 38 patients who received the comparator, tranexamic acid. Adverse reactions for icatibant injection were similar in nature and frequency to those reported in Table 1.

In all three Phase III trials, patients were eligible for icatibant injection treatment of subsequent attacks in an open-label extension. Patients were treated with icatibant injection 30 mg and could receive up to 3 doses of icatibant injection 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 icatibant injection 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 icatibant injection-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 icatibant injection. One patient experienced non-serious adverse reactions of generalized pruritus (moderate in severity) and generalized cutaneous burning sensation approximately 5 hours after injection with icatibant injection 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 icatibant injection-treated attack. At the tenth treated attack, the patient experienced mild generalized pruritus following icatibant injection 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 icatibant injection in patients who self-administered icatibant injection was similar to that of patients whose therapy was administered by healthcare professionals.

Pediatric Population

A total of 32 pediatric subjects (11 pre-pubertal and 21 pubertal/post-pubertal) with HAE were exposed to treatment with icatibant injection 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 icatibant injection, 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 icatibant injection and 1 pubertal/post-pubertal patient received a single dose of icatibant injection for each of two HAE attacks (in total, two doses).

The majority of pediatric patients (N=29 [90.6%]) treated with subcutaneous icatibant injection 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 icatibant injection exposure in the 90-day clinical study period.

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 adult 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 adult patients treated with icatibant injection. See Table 1.

Overall, no clinically significant changes in laboratory values were observed in pediatric subjects following a single icatibant injection exposure in the 90-day clinical study period.

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post-marketing experience with icatibant injection. 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.
Hypersensitivity: urticaria
Product issues: drug ineffectiveness, device failure

DRUG INTERACTIONS

Overview

Formal drug-drug interaction studies have not been conducted with icatibant injection. Pharmacokinetic drug interactions involving CYP450 are not expected (see **Action and Clinical Pharmacology**, **Metabolism**). The treatment with Teva-Icatibant 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

Icatibant injection	Ref	Effect	Clinical comment
Angiotensin converting enzyme inhibitor (ACE-I) products	T	Co-administration of icatibant injection 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 icatibant injection may interfere with the mode of action of ACE-I products by blocking the bradykinin 2 receptor. Icatibant injection has been reported to attenuate the blood pressure-lowering effects of ACE-I in normotensive and hypertensive subjects.	Caution is recommended if Teva-Icatibant 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

Teva-Icatibant 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 icatibant injection. 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

Teva's Patient Support Program

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

Recommended Dose and Dosage Adjustment

Adults

The recommended dose of Teva-Icatibant for adults 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.

Children and Adolescents (aged 2 to 17 years)

The recommended dose of Teva-Icatibant based on body weight in children and adolescents is provided in Table 3 below.

Table 3 - Dosage Regimen for Pediatric Patients

Body Weight	Dose (Injection Volume)
12 kg to 25 kg	10 mg (1 mL)
26 kg to 40 kg	15 mg (1.5 mL)
41 kg to 50 kg	20 mg (2 mL)
51 kg to 65 kg	25 mg (2.5 mL)
>65 kg	30 mg (3 mL)

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

No dosage regimen can be recommended for children aged less than 2 years or weighing less than 12 kg as the safety and efficacy have not been established (see **CLINICAL TRIALS**).

Missed Dose

Not applicable.

Administration

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

Teva-Icatibant is supplied as a single-use prefilled syringe that delivers 3 mL of solution, equivalent to a 30 mg icatibant acetate dose. The syringe and needle should be discarded in a sharps container after use.

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

Teva-Icatibant 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.

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

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 Teva-Icatibant by subcutaneous injection in the abdominal area over at least 30 seconds.

Adult patients (or their caregivers) may self-administer Teva-Icatibant upon recognition of symptoms of an HAE attack. They should be trained in subcutaneous injection techniques by a healthcare professional before they can administer Teva-Icatibant. The first administration of Teva-Icatibant should be performed under the guidance of a healthcare professional before beginning the self-administration of Teva-Icatibant. Self-administration training is also available to adult patients and caregivers directly through Teva's Patient Support Program.

Pediatric Patients
Teva-Icatibant may be administered to children and adolescents (≥2 to <18 years) by a healthcare professional. Teva-Icatibant 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 Teva-Icatibant. Ensure patients have received adequate training in the preparation of the empty graduated syringe, measurement of the correct dose of Teva-Icatibant, and transfer of the dose to the graduated syringe. Self-administration training is also available directly through Teva's Patient Support Program.

The required injection volume in mL (derived from Table 3) 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 Teva's Patient Support Program.

Elderly Patients
Patients >65 years of age are likely to have increased systemic exposure to Teva-Icatibant 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, 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 immediately.

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 B_2 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 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.

Pharmacokinetics

Table 4 - Summary of Icatibant's Pharmacokinetic Parameters in Healthy Adult Subjects Following Subcutaneous Administration

	C_{max}	$t_{½}$ (h)	AUC_{0-4}	Clearance	Volume of distribution
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 icatibant injection 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 ($AUC_{0-\infty}$) 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
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 icatibant injection.

STORAGE AND STABILITY

Store at 2 to 25°C; do not freeze.

SPECIAL HANDLING INSTRUCTIONS

The solution should be clear and colourless and free from visible particles. Prefilled 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

Adult Patients
Teva-Icatibant 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 also be obtained through Teva's Patient Support Program.

Pediatric Patients
Pediatric patients receive the same carton as adult patients that supplies Teva-Icatibant as a sterile solution for subcutaneous injection in a single-use prefilled syringe. Pediatric subjects must also obtain a separate patient self-administration kit. The kit, which contains a travel case, needle protection devices, connectors, graduated syringes, and alcohol wipes, can be obtained through Teva's Patient Support Program.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

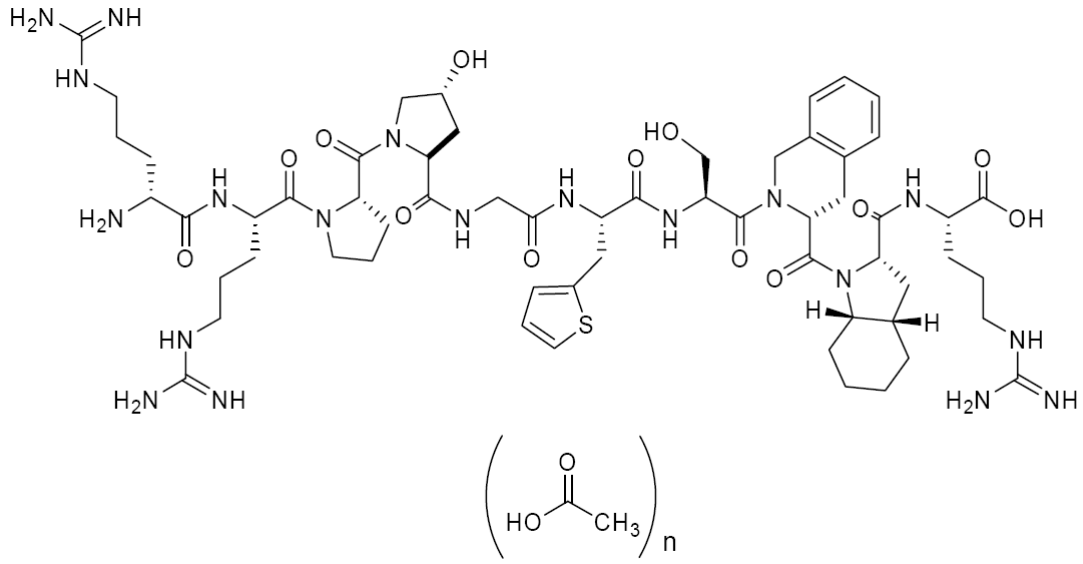
Drug Substance

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 Icatibant base [60.03 g/mol acetate]

Structural formula:



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

Icatibant Acetate is a white to off-white powder isolated by lyophilisation and existing as an acetate salt (1-4 moles of acetic acid present). It is deliquescent, soluble in water, phosphate buffer pH 7.4, isotonic saline solution, acetate buffer pH 3.5, ethanol and methanol. Polymorphic forms are not described in literature and it can be concluded that only amorphous form of Icatibant Acetate exists and is known.

CLINICAL TRIALS

Study demographics and trial design

Table 5- 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	icatibant injection 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	icatibant injection 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	icatibant injection 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	icatibant injection 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	icatibant injection 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	icatibant injection 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
	Entire Study		84	36.6 years (18 to 65)	27 male; 57 female
Study 3 (FAST 2, JE049 #2102)	Randomized, double-blind, active-controlled:	icatibant injection 30 mg/3 mL SC x 1 dose or tranexamic acid PO TID for 2	74	41.1 years (19 to 68)	27 male; 47 female

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
	Patients with moderate to severe abdominal or cutaneous attacks	days plus a placebo matched to the alternate therapy.			
	Open-label: Patients with any laryngeal attack	icatibant injection 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	icatibant injection 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	icatibant injection 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	icatibant injection 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 icatibant injection 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 icatibant injection 30 mg or placebo by subcutaneous injection. Patients with severe laryngeal attacks of HAE were not randomized and received open-label icatibant injection 30 mg SC. In the open-label extension phase of the study, patients were eligible for treatment of subsequent attacks with icatibant injection 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 icatibant injection 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 icatibant injection 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 icatibant injection 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 icatibant injection (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 6 below.

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

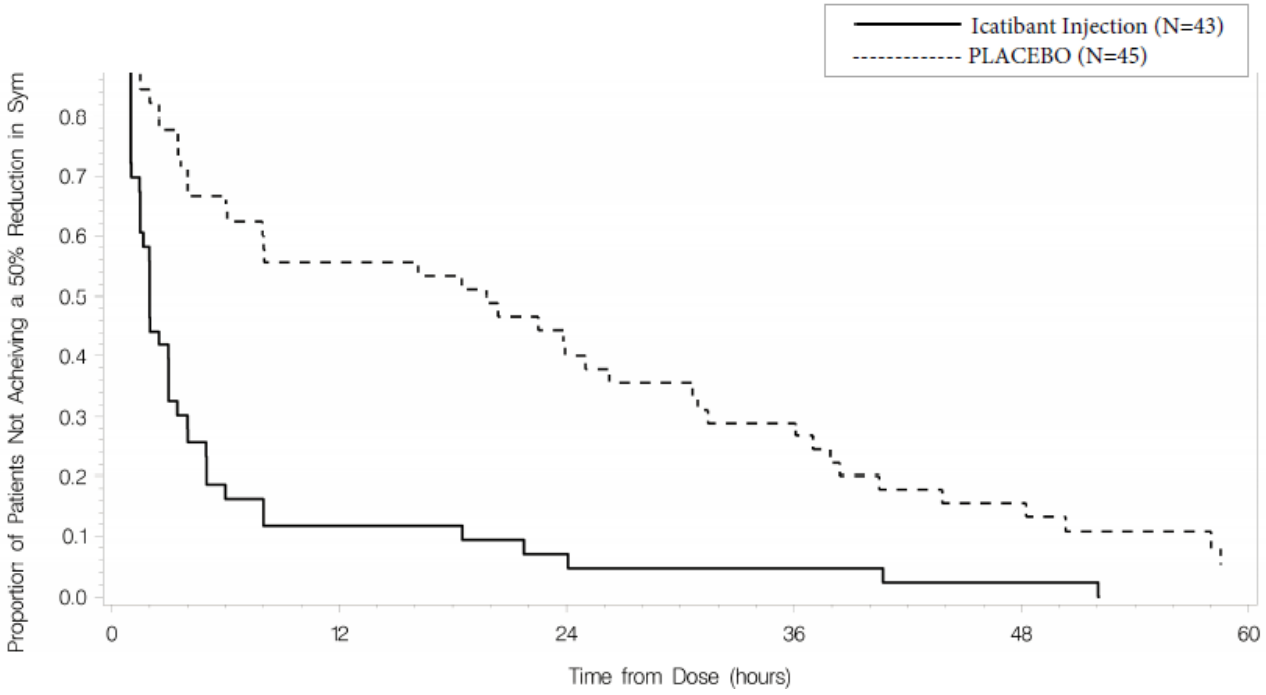


Table 6 - Results of studies 1, 2, and 3 in the non-laryngeal ITT population

Study 1	**Statistic**	**Icatibant Injection (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**	**Icatibant Injection (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**	**Icatibant Injection (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)[ae]	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: icatibant injection n=26, Placebo n=27; Study 3: Icatibant Injection 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 icatibant injection 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 icatibant injection. In the first 15 icatibant injection 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 icatibant injection 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 icatibant

injection treatment can reduce the risk of suffocation and mortality in HAE patients with laryngeal attacks.

Table 7 - Results of Study 1 in the laryngeal treated population (post-hoc analysis)

Endpoints	Statistic	Icatibant Injection (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 icatibant injection by patients who experienced acute attacks of HAE was assessed in the open-label uncontrolled Study 4. Patients who self-administered icatibant injection 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 8 - 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 icatibant injection 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 icatibant injection 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.

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 cardio-protective 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 icatibant injection 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 subcutaneous 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 subcutaneous 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 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).

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

REFERENCES

1. FIRAZYR® Product Monograph, Takeda Canada Inc., Revision date December 14, 2020, Submission Control No. 241943.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

[Pr]Teva-Icatibant
icatibant injection

Read this carefully before you start taking Teva-Icatibant and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Teva-Icatibant.

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

What is Teva-Icatibant used for?
Teva-Icatibant is used to treat acute attacks of hereditary angioedema (HAE) in:
- adults,
- adolescents, and
- children aged 2 years and older

with a deficiency of a protein called C1-esterase inhibitor.

How does Teva-Icatibant work?
In HAE, levels of a substance in your bloodstream called bradykinin are increased. This can cause swelling, pain, nausea, and diarrhea. Teva-Icatibant blocks the activity of bradykinin. This stops the symptoms of an HAE attack from getting worse.

What are the ingredients in Teva-Icatibant?
Medicinal ingredient: icatibant, as icatibant acetate
Non-medicinal ingredients: acetic acid glacial, sodium chloride, sodium hydroxide and water for injection

Teva-Icatibant comes in the following dosage forms:
Solution for injection, 30 mg / 3 mL (10 mg / mL)

Do not use Teva-Icatibant if:
- you or your child 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 Teva-Icatibant. 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 or your child with Teva-Icatibant.

Caregivers/Self-administration:

- You or your child's first injection of Teva-Icatibant 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 Teva-Icatibant only after receiving training on how to use it. A healthcare professional will teach you and your caregiver how to use it.
- Self-injection for children is not recommended. Teva-Icatibant 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 or your child have a laryngeal HAE attack:
- inject Teva-Icatibant, 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:

- Teva-Icatibant 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 icatibant injection 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 icatibant injection use are not known.
- Early studies have shown that when icatibant injection 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 Teva-Icatibant will harm your unborn baby. If you are pregnant or planning to become pregnant, speak to your doctor before using Teva-Icatibant. You and your doctor will decide if Teva-Icatibant is right for you.

- It is not known if Teva-Icatibant passes into breast milk. If you are breast-feeding or planning to breast-feed, speak to your doctor before using Teva-Icatibant about the best way to feed your baby.

Driving and Using Machinery

- Teva-Icatibant may cause tiredness, dizziness or sleepiness. DO NOT drive or operate machinery after using Teva-Icatibant 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 Teva-Icatibant:

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

How to take Teva-Icatibant:

- You or your caregiver may inject Teva-Icatibant only after receiving training on how to use it.
- Always use Teva-Icatibant exactly as your healthcare professional has shown you.
- Be sure to use each Teva-Icatibant prefilled syringe only once, even if there is still medicine in it.
- Teva-Icatibant 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 Teva-Icatibant 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 Teva-Icatibant will need to be transferred from the prefilled syringe into an empty graduated syringe. This graduated syringe will then be used to inject Teva-Icatibant.

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

Usual dose:

All Patients:

- Take Teva-Icatibant as soon as you or your child have symptoms of an HAE attack. Symptoms can include swelling, pain, nausea, and diarrhea.
- **If you or your child have a laryngeal HAE attack, inject Teva-Icatibant 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 Teva-Icatibant 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 doctor 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 Teva-Icatibant 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 Teva-Icatibant 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 Teva-Icatibant.

Read these instructions before using Teva-Icatibant and each time you or your child gets 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 Teva-Icatibant. Ask your healthcare professional any questions you may have. Do not attempt to inject Teva-Icatibant until you are sure how to and your doctor has determined that it is appropriate for you to do so.

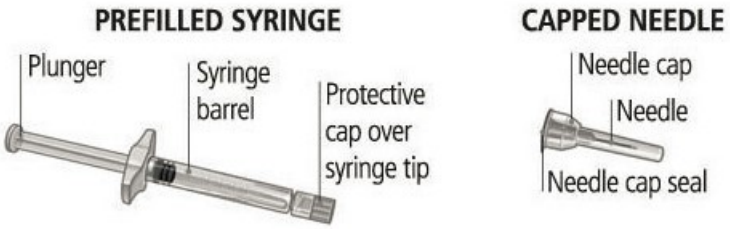
Teva's Patient Support Program has been set up to provide guidance and additional training on how to use Teva-Icatibant. It will give you information and answer any questions you may have. Teva-Icatibant and supplies needed to give it are provided through this Program. Information including training can be obtained through the Program by calling Teva Canada Limited at 1-800-268-4127 ext. 3.

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 Teva-Icatibant prescription:

1) Your Teva-Icatibant carton, which includes:
- One single-use prefilled syringe (containing 3 mL of Teva-Icatibant solution).
- One capped needle.



2) The administration supplies, which include(s):
- One alcohol wipe.

- **For Adolescents (weighing 65 kg or less) and Children (Aged 2 years and above),**
  - The following supplies are needed to measure out and transfer the dose:
    - One 3 mL graduated syringe.
    - One connector.

Not provided with Teva-Icatibant:

3) A sharps disposal container.
If you do not have a sharps disposal container, you may use a household container that is:
- 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 Teva-Icatibant	**ALL PATIENTS** **Adults, Adolescents and Children (Aged 2 years and above)**

- 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 Teva-Icatibant prefilled syringe to make sure:
    - 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.

If any of the above are not met:

- **do not use the syringe, and**
- **go to the nearest hospital emergency room to seek medical help right away.**

- Hold the Teva-Icatibant prefilled syringe firmly.
- Remove the protective cap from the end of the Teva-Icatibant prefilled syringe.
- Put down the Teva-Icatibant prefilled syringe on the clean work surface.

Adults and Adolescents (weighing more than 65 kg):

- Skip Step 3, and
- **Proceed to Step 4.**

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

- **Proceed to Step 3.**

Step 3 – Preparing the Graduated Syringe – Measuring out and transferring the dose from the Teva-Icatibant prefilled syringe	ADOLESCENTS (weighing 65 kg or less) and CHILDREN (Aged 2 years and above)

A) Preparing the Empty Graduated Syringe and Connector

- Remove the caps on each end of the connector.

Avoid touching the ends of the connector and syringe tips to prevent contamination.

- Screw the connector onto the Teva-Icatibant prefilled syringe.
- Attach the graduated syringe to the other end of the connector. Make sure that both connections fit securely.

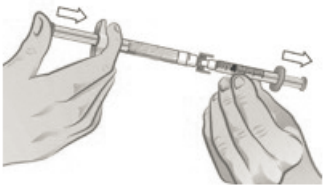
B) Transferring Teva-Icatibant to the Empty Graduated Syringe

- Use the table below to determine how much Teva-Icatibant 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 mL
26 kg to 40 kg	1.5 mL
41 kg to 50 kg	2 mL
51 kg to 65 kg	2.5 mL

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



- If the Teva-Icatibant solution does not begin to transfer to the graduated syringe, pull slightly on the plunger of the graduated syringe. Do this until the Teva-Icatibant 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:

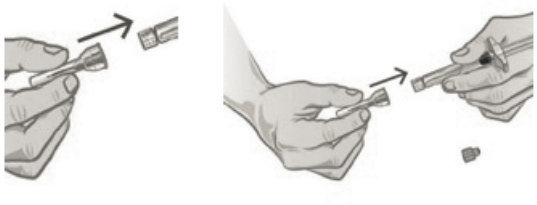
- Remove the Teva-Icatibant prefilled syringe and connector from the graduated syringe.
- Put down the graduated syringe on the clean work surface.
- Discard the Teva-Icatibant prefilled syringe and connector into a sharps disposal container.
  Be sure to use each Teva-Icatibant prefilled syringe only 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)**

- Remove the seal from the needle cap. Keep the needle inside the protective needle cap until ready to use.

- Grip the syringe firmly.
  - For adults and adolescents weighing more than 65 kg: The syringe is the Teva-Icatibant prefilled syringe.
  - For adolescents weighing less than 65 kg and children: The syringe is the graduated syringe.

- Carefully attach the needle to the syringe.



- Firmly screw the needle on the syringe containing the Teva-Icatibant 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)**

- 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.

- Clean the Teva-Icatibant injection site with an alcohol wipe and allow it to dry.

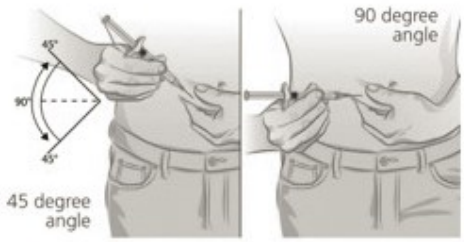
Step 6 – Injecting Teva-Icatibant	**ALL PATIENTS** **Adults, Adolescents and Children (Aged 2 years and above)**

- Remove the needle from the needle cap by holding the needle cap and carefully pulling the syringe. Do NOT pull up on the plunger.

- Hold the syringe in one hand, between your fingers and thumb.

- 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.

- 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 Teva-Icatibant 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 have taken too much Teva-Icatibant, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using Teva-Icatibant?

These are not all the possible side effects you may feel when taking Teva-Icatibant. If you experience any side effects not listed here, contact 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

Teva-Icatibant may affect certain liver enzyme levels in your blood. Your doctor will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking 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 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			X
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, talk to 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 Teva-Icatibant 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 Teva-Icatibant:

- 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://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website http://www.tevacanada.com; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.
- For information about Teva's Patient Support Program, contact Teva Canada Limited at 1-800-268-4127 ext. 3.

This leaflet was prepared by Teva Canada Limited, Toronto, Ontario M1B 2K9

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