PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrMINT-ICATIBANT

icatibant injection

Solution, 30 mg / 3 mL (10 mg / mL) as icatibant acetate Single-Use Prefilled Syringe, Subcutaneous
Drugs used in hereditary angioedema

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[Pr]MINT-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, Water for injections .

INDICATIONS AND CLINICAL USE

MINT-ICATIBANT (icatibant acetate) is indicated for the treatment of acute attacks of hereditary angioedema (HAE) in adults and adolescents who weigh more than 65 kg with C1-esterase inhibitor deficiency.

Patients or a caregiver should be trained in subcutaneous injection techniques under the guidance of a healthcare professional before they can administer MINT-ICATIBANT (see **DOSAGE AND ADMINISTRATION**).

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

Pediatrics (<18 years of age):
MINT-IBATICANT is indicated for use in adolescents who weigh more than 65 kg.

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

MINT-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 MINT-ICATIBANT. The first self-administration of MINT-ICATIBANT should be performed under the guidance of a healthcare professional. Administration of MINT-ICATIBANT to 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 MINT-ICATIBANT (see **DOSAGE AND ADMINISTRATION**). 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 **CLINICAL TRIALS**).

Cardiovascular

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

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

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

Pediatrics (< 18 years of age)
MINT-ICATIBANT is indicated for use in adolescents who weigh more than 65 kg.

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

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

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

Pediatric Population

The majority of pediatric patients (90.6%) who were treated with subcutaneous icatibant 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 dosing. Other adverse reactions reported by patients treated with icatibant (≥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 administered subcutaneously.

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

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

	Icatibant (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 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 were similar in nature and frequency to those reported in Table 1.

In all three Phase III trials, patients were eligible for icatibant treatment of subsequent attacks in an open-label extension. Patients were treated with icatibant 30 mg and could receive up to 3 doses of icatibant 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 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-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. 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 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-treated attack. At the tenth treated attack, the patient experienced mild generalized pruritus following icatibant 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 in patients who self-administered icatibant 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 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, 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 and 1 pubertal/post-pubertal patient received a single dose of icatibant for each of two HAE attacks (in total, two doses).

The majority of pediatric patients (N=29 [90.6%]) treated with subcutaneous icatibant 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 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. See Table 1.

Overall, no clinically significant changes in laboratory values were observed in pediatric subjects following a single icatibant 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. 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. Pharmacokinetic drug interactions involving CYP450 are not expected (see **Action and Clinical Pharmacology**, **Metabolism**). The treatment with 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	Ref	Effect	Clinical comment
Angiotensin converting enzyme inhibitor (ACE-I) products	T	Co-administration of icatibant 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 may interfere with the mode of action of ACE-I products by blocking the bradykinin 2 receptor. Icatibant has been reported to attenuate the blood pressure-lowering effects of ACE-I in normotensive and hypertensive subjects.	Caution is recommended if 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

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

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

MINT-ICATIBANT is indicated for use in adults and adolescents who weigh more than 65 kg. Children and adolescents who weigh 65 kg or less should use an alternative icatibant injection product.

Adults
The recommended dose of MINT-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.

Adolescents (weighing more than 65 kg)
The recommended dose of MINT-ICATIBANT in adolescents is 30 mg (3.0 mL).

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

Missed Dose

Not applicable.

Administration

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

MINT-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.

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

MINT-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 MINT-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 MINT-ICATIBANT by subcutaneous injection in the abdominal area over at least 30 seconds.

Adult patients (or their caregivers) may self-administer MINT-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 MINT-ICATIBANT. The first administration of MINT-ICATIBANT should be performed under the guidance of a healthcare professional before beginning the self-administration of MINT-ICATIBANT.

Pediatric Patients
MINT-ICATIBANT may be administered to adolescents (<18 years) by a healthcare professional. MINT-ICATIBANT may also be self-administered, if appropriate, or administered by a caregiver only after

training in subcutaneous injection technique by a healthcare professional.

Elderly Patients
Patients >65 years of age are likely to have increased systemic exposure to 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

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

Pharmacodynamics

Following bradykinin challenge, development of bradykinin-induced hypotension, vasodilation, and reflex tachycardia was prevented in healthy young 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 3 - Summary of Icatibant's Pharmacokinetic Parameters in Healthy Adult Subjects Following Subcutaneous Administration

	C_{max}	$t_{½}$ (h)	AUC_{0-}	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 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.

STORAGE AND STABILITY

Store at 5°C 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
MINT-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 rubber plunger stopper, a polystyrene plunger rod a Luer-lock with a screw tip cap, and a polypropylene backstop. A hypodermic needle (25 G; 16 mm) is included in the pack.

The carton includes one prefilled syringe with one needle.

Pediatric Patients
Pediatric patients receive the same carton as adult patients that supplies MINT-ICATIBANT as a sterile

solution for subcutaneous injection in a single-use prefilled syringe.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

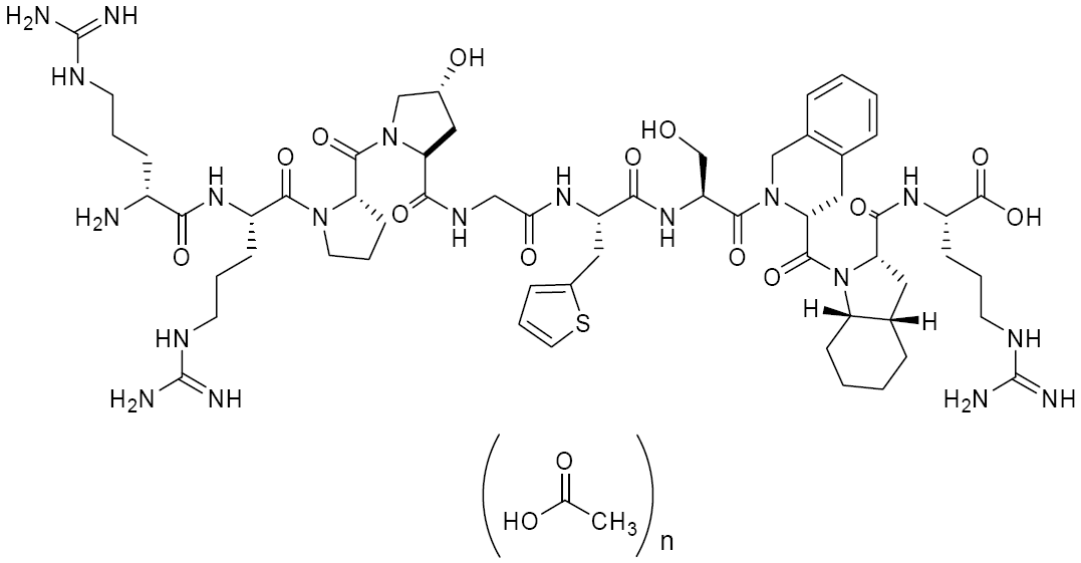
Drug Substance

Common name: icatibant acetate

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

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

Structural formula:



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

Solubility properties: Icatibant acetate is soluble in water, methanol, and dimethyl sulfoxide and insoluble in acetonitrile and dimethyl formamide.

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 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 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 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 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 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 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 #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Study 3 (FAST 2, JE049 #2102)	Randomized, double-blind, active-controlled: Patients with moderate to severe abdominal or cutaneous attacks	Icatibant 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	Icatibant 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 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 30 mg/3 mL SC x 1 dose.	104	41.6 years (18 to76)	36 male; 68 female
	HCP Administration: Any attack severe enough to warrant treatment.		23	44.0 years (19 to 76)	8 male; 15 female
	Self-administration: Any attack severe enough to warrant treatment		98	40.8 years (18 to 76)	33 male; 65 female
Study 5 (HGT-FIR-086)	Open-label Any cutaneous, abdominal, or laryngeal symptoms of an acute attack	Icatibant 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 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 30 mg or placebo by subcutaneous injection. Patients with severe laryngeal attacks of HAE were not randomized and received open label icatibant 30 mg SC. In the open-label extension phase of the study, patients were eligible for treatment of subsequent attacks with icatibant 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 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 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 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 (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 5 below.

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

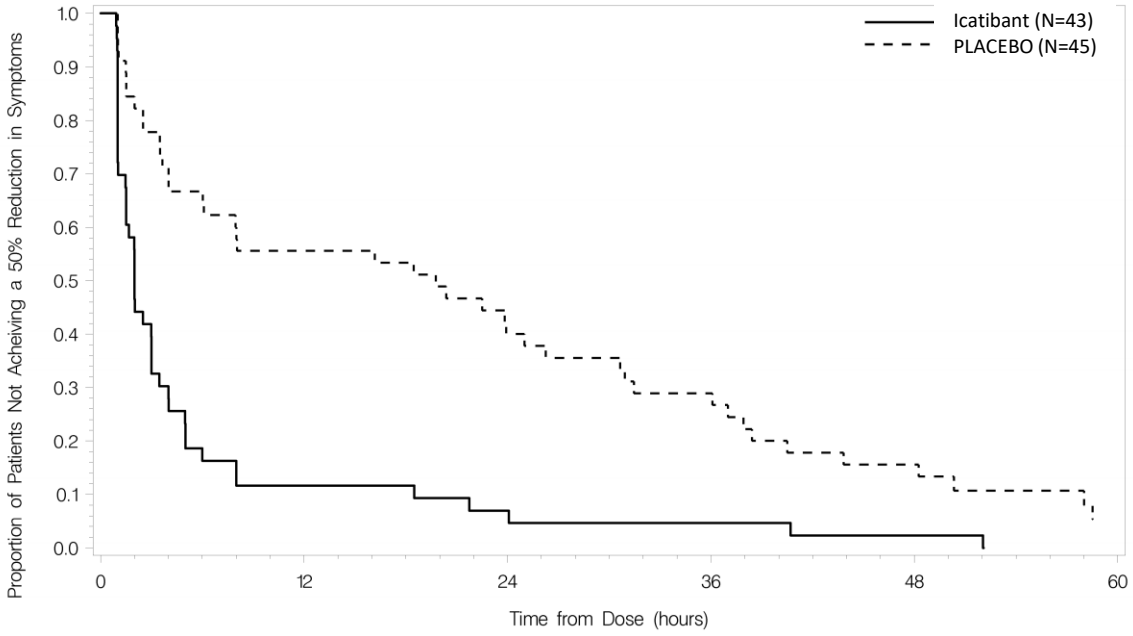


Table 5 - Results of studies 1, 2, and 3 in the non-laryngeal ITT population

Study 1	Statistic	Icatibant (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
Study 1	**Statistic**	**Icatibant (n = 43)**	**Placebo (n = 45)**
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 (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 (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	Median	10.0	51.0
Symptom Relief (hours) [d]	p-value	<0.001	
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 n=26, Placebo n=27; Study 3: Icatibant 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 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. In the first 15 icatibant 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 with a control arm are not available for most of the patients with laryngeal attacks. In study 1, 27 patients completed laryngeal symptom assessments using a 5-item composite visual analog score (VAS-5). Post-hoc analyses of these efficacy data are shown in Table 6 below. The median time to onset of symptom relief (2.0 hours) was similar to those observed for the non-laryngeal attacks in studies 1, 2 and 3 (2.0 to 2.3 hours). This was reflected by similar median times to onset of symptom relief for the individual laryngeal symptoms of difficulty swallowing (1.8 hours) and voice change (1.7 hours). No formal studies have been conducted to determine if icatibant treatment can reduce the risk of suffocation and mortality in HAE patients with laryngeal attacks.

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

Endpoints	**Statistic**	**Icatibant** (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)
Endpoints	**Statistic**	**Icatibant** (n = 27)
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)
Endpoints	**Statistic**	**Icatibant** (n = 27)
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 by patients who experienced acute attacks of HAE was assessed in the open-label uncontrolled Study 4. Patients who self-administered icatibant 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 7 shows the efficacy results for Study 5.

Table 7 - 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 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 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 cardioprotective effects of bradykinin, and antagonism of this receptor could potentially have negative cardiovascular effects during reperfusion after acute ischemia. Icatibant decreased coronary blood flow in the isolated guinea pig heart and aggravated the duration of post-ischemic reperfusion arrhythmias in the isolated rat heart. Intracoronary infusion of icatibant in an anesthetized myocardial infarction dog model increased mortality rate 2-fold over saline infusion. Icatibant does not cause cardiac conduction changes in vitro using the *Xenopus* oocyte model, nor does it have significant effects on HERG-mediated outward current in CHO cells at concentrations up to 300 µM. Icatibant did not elicit any cardiac conduction changes or in vivo in normal dogs or in various dog models (ventricular pacing, physical exertion and coronary ligation) where no associated hemodynamic changes were observed.

Based on animal data there is a theoretical potential that antagonism of the B2 receptor can lead to myocardial ischemia. Myocardial ischemic events have been reported infrequently in post-marketing experience with icatibant 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 day.

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., Date of Revision: December 14, 2020; Control Number 241943.

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

PrMINT-ICATIBANT
icatibant injection

Read this carefully before you start taking MINT-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 MINT-ICATIBANT.

What is MINT-ICATIBANT used for?
MINT-ICATIBANT is used to treat acute attacks of hereditary angioedema (HAE) in:
- Adults and
- adolescents who weigh more than 65 kg

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

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

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

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

Do not use MINT-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 MINT-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 MINT-ICATIBANT.

Caregivers/Self-administration:
- You or your child's first injection of MINT-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 MINT-ICATIBANT only after receiving

training on how to use it. A healthcare professional will teach you and your caregiver how to use it.
- 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 MINT-ICATIBANT, and
  - go to the nearest hospital emergency room for medical help right away.
- A blockage of the airway may occur faster in adolescents than in adults. This is because the airway passage is smaller in these patients.

Adolescents (weighing more than 65 kg):
- There is limited experience with the use of MINT-ICATIBANT in the treatment of:
  - laryngeal HAE attacks in adolescents

Effects on Reproductive Organs in Adolescents and Children
- The effects of long-term icatibant use are not known.
- Early studies have shown that when icatibant 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 reproductive organs are working.

Pregnancy and Breastfeeding:
- It is not known if icatibant will harm your unborn baby. If you are pregnant or planning to become pregnant, speak to your doctor before using MINT-ICATIBANT. You and your doctor will decide if MINT-ICATIBANT is right for you.
- It is not known if icatibant passes into breast milk. If you are breast-feeding or planning to breast-feed, speak to your doctor before using MINT-ICATIBANT about the best way to feed your baby.

Driving and Using Machinery
- MINT-ICATIBANT may cause tiredness, dizziness or sleepiness. DO NOT drive or operate machinery after using MINT-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 MINT-ICATIBANT:
- Angiotensin converting enzyme (ACE) inhibitor (used to lower blood pressure)

How to take MINT-ICATIBANT:
- You or your caregiver may inject MINT-ICATIBANT only after receiving training on how to use it.
- Always use MINT-ICATIBANT exactly as your healthcare professional has shown you.
- Be sure to use each MINT-ICATIBANT prefilled syringe only once, even if there is still medicine in it.

- MINT-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 MINT-ICATIBANT prefilled syringe will be used to give the injection.

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

Usual dose:

All Patients:

- Take MINT-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 MINT-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 MINT-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 MINT-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 and children weighing 65 kg or less should use an alternative icatibant injection product.

STEP-BY-STEP INSTRUCTIONS FOR INJECTION:

This section contains information on how to give an injection of MINT-ICATIBANT.

Read these instructions before using MINT-ICATIBANT and each time you gets a repeat prescription. There may be new information.

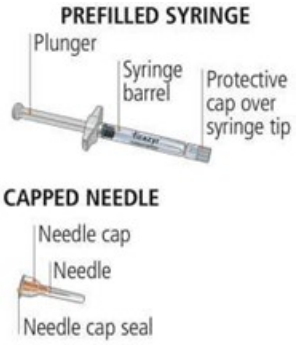
These instructions are not meant to take the place of training by a healthcare professional. A healthcare professional will teach you and your caregiver how to give MINT-ICATIBANT. Ask your healthcare professional any questions you may have. Do not attempt to inject MINT-ICATIBANT until you are sure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

Step 1 – Gather supplies	ALL PATIENTS Adults and Adolescents (weighing more than 65 kg)

Collect the following listed items to prepare and give the injection:

Items provided to you with your MINT-ICATIBANT prescription:

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



2) The administration supplies, which include:
- Alcohol wipes

Not provided with MINT-ICATIBANT:
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 MINT-ICATIBANT	ALL PATIENTS Adults and Adolescents (weighing more than 65 kg)

- 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 MINT-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.

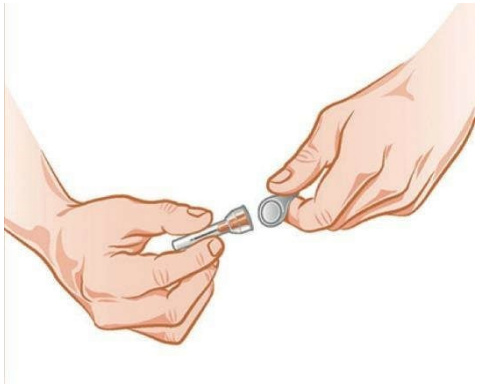
If any of the above are not met:

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

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

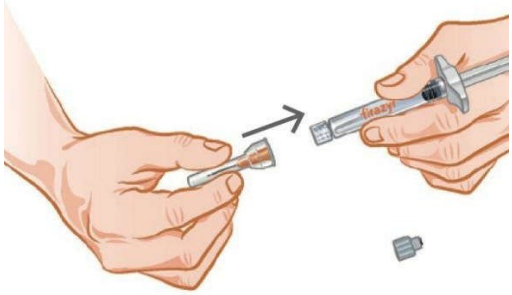
Step 3 – Preparing the syringe and the needle for injection	**ALL PATIENTS** **Adults and Adolescents (weighing more than 65 kg)**

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

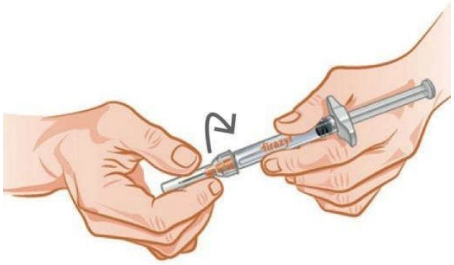


- Grip the syringe firmly.
  - For adults and adolescents weighing more than 65 kg: The syringe is the MINT-ICATIBANT prefilled syringe.

- Carefully attach the needle to the syringe.

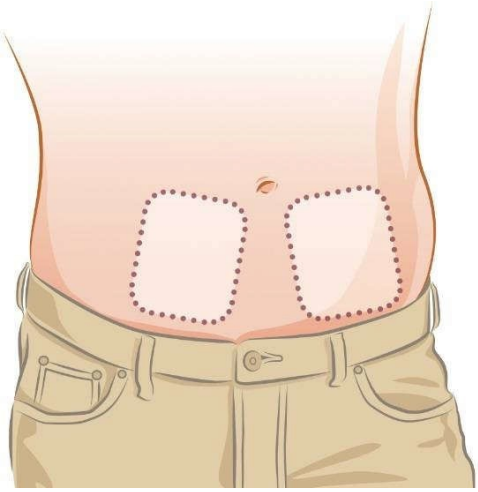


- Firmly screw the needle on the syringe containing the MINT-ICATIBANT dose. Be careful not to remove the needle from the needle cap.



Step4 – Preparing the injection site	**<u>ALL PATIENTS</u> Adults and Adolescents (weighing more than 65 kg)**

- 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.



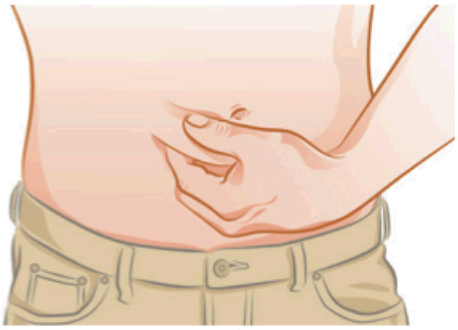
- Clean the MINT-ICATIBANT injection site and allow it to dry.

Step 5 – Injecting MINT-ICATIBANT	ALL PATIENTS Adults and Adolescents (weighing more than 65 kg)

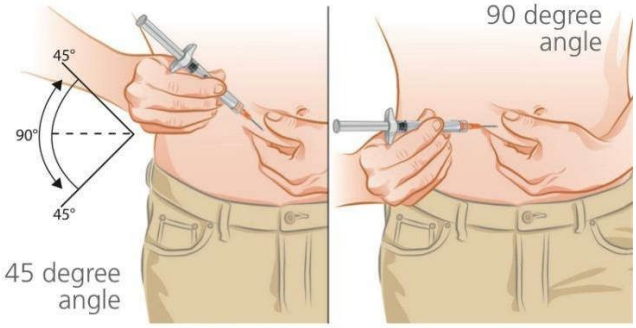
- Remove the needle from the needle cap by holding the needle cap and carefully pulling the syringe. Do NOT pull up on the plunger.

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

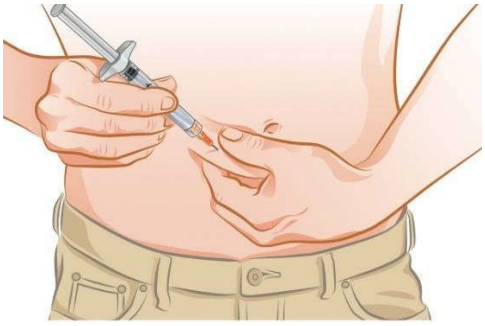
- Use your other hand to gently pinch the fold of skin you cleaned with the alcohol wipe between your thumb and fingers for your injection.



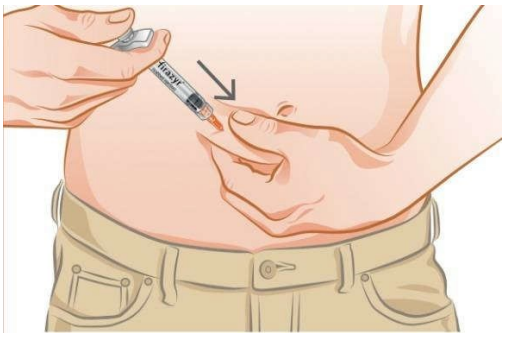
- Hold the syringe between a 45 to 90 degree angle to the skin with the needle facing the fold of skin you are holding.



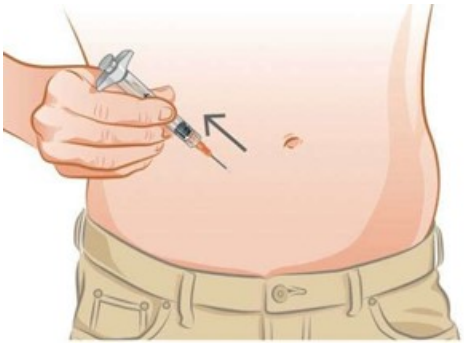
- Hold the fold of skin. Bring the syringe to the skin and quickly insert the needle into the skin fold.



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

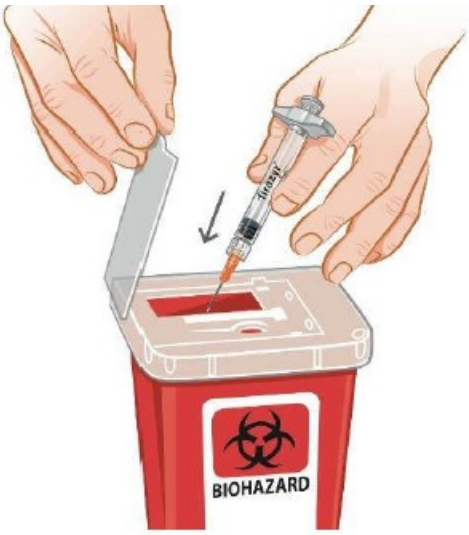


- Release the skin fold and gently pull the needle out.



Step 6 – Disposing of your syringe	<u>ALL PATIENTS</u> **Adults and Adolescents (weighing more than 65 kg)**

- 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 MINT-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 MINT-ICATIBANT?

These are not all the possible side effects you may feel when taking MINT-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

MINT-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

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	
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 (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) 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 5°C to 25°C.
- Do not freeze.
- Store MINT-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 MINT-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 (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.mintpharmaceuticals.com, or by calling 1-877-398-9696.

This leaflet was prepared by Mint Pharmaceuticals Inc.

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