NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Icatibant Lupin 30 mg/3 mL solution for injection pre-filled syringe.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe of 3 mL contains icatibant acetate equivalent to 30 mg icatibant.

Each mL of the solution contains 10 mg of icatibant.

For the full list of excipients, see **Section 6.1 List of Excipients**.

3 PHARMACEUTICAL FORM

Solution for injection.

Icatibant Lupin is supplied as a sterile solution for injection in single use pre-filled syringes. The solution should be clear and colourless and free from visible particles. The pH of the injection is approximately 5.5.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Icatibant Lupin is indicated for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults, adolescents and children aged 2 years and older with C1-esterase-inhibitor deficiency.

4.2 Dose and Method of Administration

Dose

Adults

The recommended dose of Icatibant Lupin for adults is one subcutaneous injection of 30 mg.

In the majority of cases a single injection of Icatibant Lupin is sufficient to treat an attack. In case of insufficient relief or recurrence of symptoms, a second injection of Icatibant Lupin can be administered after 6 hours. If the second injection produces insufficient relief or a recurrence of symptoms is observed, a third injection of Icatibant Lupin can be administered after a further 6 hours. No more than 3 injections of Icatibant Lupin should be administered in a 24-hour period.

In clinical trials, not more than 8 injections of Icatibant Lupin per month have been administered.

Adolescents and Children (aged 2 to 17 years)

The recommended dose of Icatibant Lupin based on body weight in children and adolescents (aged 2 to 17 years) is provided in **Table 1** below.

Table 1: Dosage Regimen for Paediatric Patients

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

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

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 this paediatric group as the safety and efficacy have not been established.

Method of Administration

Icatibant Lupin is intended for subcutaneous injection preferably in the abdominal area. Injection should be given slowly due to the volume to be administered (3 mL).

Adult patients may self-administer Icatibant Lupin upon recognition of symptoms of an HAE attack after training under the guidance of a healthcare professional. Patients who self-inject should be advised to seek urgent medical attention if there is no evidence of resolution of the HAE attack within 2 hours of self-injection, or immediately should the HAE attack progress to involve the face, lips or pharyngolaryngeal area. Patients whose initial HAE attack involves the face, lips or pharyngolaryngeal area should seek urgent medical attention, regardless of their response to Icatibant Lupin following self-injection.

Icatibant Lupin may be administered to children and adolescents (2-17 years) by a healthcare professional or caregiver only after training in subcutaneous injection technique by a healthcare professional.

Patients with laryngeal symptoms should seek medical attention immediately after administration of Icatibant Lupin and need to be managed in an appropriate medical institution after injection until the physician considers discharge to be safe. Icatibant Lupin contains no antimicrobial agent and should be used immediately. Each syringe is intended for single use in one patient only. Any residue should be discarded.

Hepatic Impairment

No dosage adjustment is required in patients with hepatic impairment.

Renal Impairment

No dosage adjustment is required in patients with renal impairment.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special Warnings and Precautions for Use

Ischaemic Heart Disease

Icatibant did not elicit any cardiac conduction change *in vitro* (hERG channel) or *in vivo* in normal dogs or in dogs undergoing physical exertion. Icatibant has been shown to aggravate induced cardiac ischaemia in several non-clinical models, including a study in dogs involving coronary ligation, probably as a result of left ventricular failure. Bradykinin and the B2 receptors have been shown to have cardioprotective properties in animals, which were attenuated by icatibant.

Under ischaemic conditions, a deterioration of cardiac function and a decrease in coronary blood flow could theoretically arise from antagonism of the B2 receptor.

Caution should therefore be observed in the administration of icatibant to patients with acute ischaemic heart disease or unstable angina pectoris.

Stroke

There is a theoretical possibility that icatibant may attenuate the positive late phase neuroprotective effects of bradykinin. Accordingly, caution should be observed in the administration of icatibant to patients in the weeks following a stroke.

Use in 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.

Use in 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.

Use in the Elderly

Limited information is available for icatibant in patients older than 65 years of age. Elderly patients have been shown to have increased systemic exposure to icatibant in limited number of elderly healthy subjects. Overall, no trends were seen with regard to the proportion of patients reporting adverse events by age group in the clinical studies and the safety profile was similar to experience in patients younger than 65.

Paediatric Use

The safety and efficacy of icatibant have not been established in children less than 2 years of age or weighing less than 12 kg.

4.5 Interactions with Other Medicines and Other Forms of Interactions

Pharmacokinetic drug interactions involving CYP450 are not expected (see **Section 5.2 Pharmacokinetic Properties**).

Co-administration of icatibant with angiotensin-converting enzyme (ACE) inhibitors has not been studied. There is a theoretical risk that icatibant may antagonise the effects of ACE inhibitors. Patients with HAE should not be taking these drugs as they can induce and exacerbate HAE attacks.

4.6 Fertility, Pregnancy and Lactation

Effects on Fertility

In a study of 39 healthy adult men and women (confined to the follicular phase of the menstrual cycle) treated with either placebo or 30 mg every 6 hours for 3 doses every 3 days for a total of 9 doses with GnRH-stimulation, no clinically significant changes were found between placebo and treatment groups for female and male reproductive hormones, the concentration of luteal phase progesterone and luteal function, menstrual cycle length in females, and sperm count, motility and morphology in males. The dosing regimen used for this study is very unlikely to be sustained in the clinical setting. However, due to the fairly small study size and confinement of women to the follicular phase of their menstrual cycles, it is unclear how fully these results can be generalized to the broader population.

Intermittent icatibant treatment (twice weekly) subcutaneously for 39 weeks in dogs did not elicit toxicity in the testes, prostate, ovary, uterus or mammary gland (30-fold the anticipated clinical exposure in patients administered 240 mg icatibant per month, based on monthly AUC).

Daily subcutaneous administration of icatibant in mature rats and dogs for 26 and 39 weeks, respectively, caused atrophy of the testes, prostate, and uterus, and masculinization of the mammary glands. In rats, atrophy of the testes and prostate, testes germinal epithelial degeneration, hypospermia, and decreased testosterone levels occurred at ≥19-fold the anticipated clinical exposure, based on monthly AUC, and atrophy of the uterus, mammary gland masculinization, and decreased luteinizing hormone levels occurred at ≥69-fold the anticipated clinical exposure, based on monthly AUC. In dogs, reduced sperm counts and atrophy of the uterus and ovaries occurred at 9-fold the anticipated clinical exposure, based on monthly AUC, and atrophy of the testes, prostate, uterus, ovaries and mammary glands, and decreased testosterone and follicle stimulating hormone levels occurred at 134-fold the anticipated clinical exposure, based on monthly AUC.

Daily subcutaneous administration of icatibant to juvenile rats caused atrophy of the testes and prostate at ≥10-fold the anticipated clinical exposure, based on monthly AUC, delayed male sexual maturation, decreased sperm counts and slight atrophy of the uterus at ≥9 mg/kg/day, and impaired male fertility at 109-fold the anticipated clinical exposure, based on monthly AUC. These effects were partly/fully reversible. Sexual maturation was also reversibly delayed in immature dogs and appeared to be secondary to changes in gonadotropin levels. Most of these effects were fully reversible over 4 weeks recovery.

Reproductive toxicity studies in adult male mice and rats with daily icatibant subcutaneous administration showed no effects on fertility at doses up to 53-fold the anticipated clinical exposure, based on monthly AUC.

Use in Pregnancy

Category C

For icatibant, no clinical data on exposed pregnancies are available.

Bradykinin B2 receptors have been shown to be present in tissues of the female reproductive system in animals and humans, and are likely to be involved in implantation and parturition.

There was an increase in pre-implantation loss in female rats treated with 10 mg/kg/day and post-implantation loss in rabbits treated with 10 mg/kg/day icatibant subcutaneously (respectively 30- and 50-fold the anticipated clinical exposure in patients administered 240 mg icatibant per month, based on monthly AUC).

Icatibant and/or its metabolites crossed the placenta in rats. Icatibant was not teratogenic when administered by subcutaneous injection during embryonic and foetal development in rats or rabbits (up to 5-fold the anticipated clinical exposure, based on monthly AUC). In rats, icatibant was associated with delayed parturition, increased foetal distress and perinatal death at 10 mg/kg/day (30-fold the anticipated clinical exposure, based on monthly AUC) and a prolonged gestation period at doses 3-fold the anticipated clinical exposure, based on monthly AUC. There were no observed adverse effects of icatibant administration during pregnancy and lactation on pup development in rats.

Therefore, icatibant should be used during pregnancy only if the potential benefit justifies the potential risk for the foetus (eg. for treatment of potentially life-threatening laryngeal attacks).

Use in Lactation

Icatibant is excreted in the milk of lactating rats at concentrations similar to those in maternal blood. No adverse effects were detected in the post-natal development of rat pups.

It is unknown whether icatibant is excreted in human breast milk, but it is recommended that breastfeeding women who take icatibant should not breastfeed for 12 hours after treatment. If breastfeeding is to be resumed, then milk should be expressed and discarded for the first 12 hours after treatment.

4.7 Effects on Ability to Drive and Use Machines

No studies of icatibant on the effects on the ability to drive and use machines have been performed. Dizziness has been reported in patients using icatibant, therefore patients should be advised not to drive or use machines if they feel dizzy. Symptoms of an HAE attack (for example, somnolence, fatigue, lethargy and tiredness) may also influence the ability to drive or use machines. Patients who experience any of the above should be advised not to drive or use machines.

4.8 Undesirable Effects

Clinical Study Experience

The safety of icatibant has been established in 1,273 subjects treated with various doses, regimens and routes of administration during Phase I-III studies in various indications.

Sixty-three HAE patients received icatibant in two Phase III trials for treatment of an attack in the controlled phase and 126 patients were treated in the open-label phase.

Almost all subjects 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 in severity, transient, and resolved without further intervention.

Table 2 lists treatment related adverse reactions reported with icatibant during the Phase III trials. Frequency is defined as: very common (≥1/10), common (≥1/100, <1/10) and uncommon (≥1/1,000 to <1/100).

Table 2: Adverse Reactions Associated with Icatibant

	Adverse Reactions		
	Very Common	**Common**	**Uncommon**
Gastrointestinal Disorders		Nausea	Vomiting
General Disorders and Administration Site Conditions	Injection site reactions*	Pyrexia	Asthenia, fatigue
Infections and Infestations			Herpes zoster, pharyngitis
Injury, Poisoning and Procedural Complications			Contusion
Investigations		Blood creatinine phosphokinase increased, prothrombin time prolonged, transaminases increased	Weight increased, blood glucose increased, liver function test abnormal
Metabolism and Nutrition Disorders			Hyperuricaemia, hyperglycaemia
Musculoskeletal and Connective Tissue Disorders			Muscle spasm
Nervous System Disorders		Dizziness, headache	
Renal and Urinary Disorders			Proteinuria
Respiratory, Thoracic and Mediastinal Disorders			Asthma, cough, nasal congestion
Skin and Subcutaneous Tissue Disorders		Rash, pruritus, erythema	Generalised urticaria
Vascular Disorders			Hot flush

* Injection site bruising, injection site haematoma, injection site burning, injection site erythema, injection site hypoesthesia, injection site irritation, injection site numbness, injection site oedema, injection site pain, injection site pressure sensation, injection site pruritus, injection site swelling, injection site urticaria and injection site warmth.

Table 3 provides the incidence of all adverse events (regardless of relationship to treatment) reported in two or more patients in the controlled phase of the Phase III studies in patients treated with icatibant, placebo or tranexamic acid.

Table 3: Incidence of Adverse Events Reported in Two or More Patients in the Controlled Phase of the Phase III Studies

Adverse Event	Icatibant (%) N=63	Placebo (%) N=29	Tranexamic Acid (%) N=38
Total Patients Reporting Adverse Events	31 (49.2)	19 (65.5)	16 (42.1)
Congenital, Familial and Genetic Disorders			
Hereditary angioedema*	14 (22.2)	5 (17.2)	6 (15.8)
Gastrointestinal Disorders			
Nausea	0	3 (10.3)	0
General Disorders and Administration Site Conditions			
Injection site pain	2 (3.2)	0	0
Injection site reaction	2 (3.2)	0	0
Pyrexia	2 (3.2)	0	0
Infections and Infestations			
Gastroenteritis	2 (3.2)	0	0
Nasopharyngitis	3 (4.8)	0	3 (7.9)
Nervous System Disorders			
Dizziness	2 (3.2)	1 (3.4)	0
Headache	2 (3.2)	2 (6.9)	2 (5.3)
Respiratory, Thoracic and Mediastinal Disorders			
Nasal congestion	2 (3.2)	0	0
Skin and Subcutaneous Tissue Disorders			
Pruritus	0	2 (6.9)	0
Rash	2 (3.2)	0	0

* HAE attacks were reported as adverse reactions, however, based on time of occurrence, the majority were recurrent attacks are not related to treatment with icatibant.

Paediatric Population

A total of 32 paediatric subjects with HAE were exposed to treatment with icatibant during the clinical study, at a dose of 0.4 mg/kg based on body weight up to a maximum dose of 30 mg. Thirty-one patients received a single dose of icatibant and 1 patient (an adolescent) received a single dose of icatibant for each of the two HAE attacks (in total, two doses).

The majority of paediatric patients who were treated with subcutaneous icatibant experienced injection site reactions such as erythema, swelling, burning sensation, skin pain and itching/pruritus. These were found to be mild to moderate in severity and consistent with reactions that have been reported in adults. Two paediatric patients experienced injection site reactions which were assessed as severe and which were completely resolved within 6 hours. These reactions were erythema, swelling, burning and warm sensation.

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

Post-marketing Experience

Table 4: Adverse Drug Reactions from Post-marketing Experience for Which the Frequency is Unknown

System Organ Class *(incidence category)*	Preferred Term
Skin and Subcutaneous Tissue Disorders *Unknown*	*Urticaria*

Immunogenicity

Across repeated treatment in the controlled Phase III HAE trials, transient positivity to anti-icatibant antibodies was observed in rare cases. All patients maintained efficacy. One icatibant-treated patient tested positive for anti-icatibant antibodies before and after treatment with icatibant. This patient was followed for 5 months and further samples were negative for anti-icatibant antibodies. No hypersensitivity or anaphylactic reactions were reported with icatibant.

No anti-icatibant antibodies were detected in paediatric patients after treatment with icatibant Reporting of suspected adverse reactions

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

No clinical information on overdose is available.

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766) in New Zealand.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Drugs used to treat hereditary angioedema.
ATC Code: B06AC02

Mechanism of Action

Hereditary angioedema (HAE), an autosomal dominant disease, is caused by an absence or dysfunction of C1-esterase-inhibitor. HAE attacks are accompanied by an increased release of bradykinin, which is the key mediator in the development of clinical symptoms.

HAE manifests as intermittent attacks of subcutaneous and/or submucosal oedema involving the upper respiratory tract, the skin and the gastrointestinal tract. An attack usually lasts between 2 to 5 days.

Icatibant is a selective competitive antagonist at the bradykinin type 2 (B2) receptor. It is a synthetic decapeptide with a structure similar to bradykinin, but with 5 non-proteinogenic amino acids. Bradykinin has been shown to be elevated during hereditary angioedema attacks and is responsible for oedema formation and related clinical symptoms of swelling and pain.

Pharmacodynamic Effects

In healthy young subjects, icatibant administered in doses of 0.8 mg/kg over 4 hours; 1.5 mg/kg/day or 0.15 mg/kg/day for 3 days, development of bradykinin-induced hypotension, vasodilatation and reflex tachycardia was prevented. Icatibant was shown to be a competitive antagonist when the bradykinin challenge dose was increased 4-fold.

Clinical Trials

Efficacy data were obtained from an initial open-label Phase II study and from two randomised, double-blind controlled multi-centre Phase III studies (one with oral tranexamic acid as the comparator and one placebo controlled). The pivotal Phase III studies were otherwise identical in design. A total of 130 patients were randomised to receive either a 30 mg dose of icatibant (63 patients) or comparator (either tranexamic acid – 38 patients, or placebo – 29 patients). Subsequent episodes of HAE were treated in an open-label extension (OLE). Patients with symptoms of laryngeal angioedema received open-label treatment with icatibant.

In the Phase III trials, the primary efficacy endpoint was median time to onset of symptom relief using a visual analogue scale (VAS) defined as absolute reduction from pre-treatment VAS of ≥20 mm if the baseline VAS was 30-50 mm or ≥30 mm if the baseline VAS was >50 mm. The FAST-2 study (JE049 #2102) demonstrated that the median time to onset of symptom relief was significantly shorter in the icatibant group than in the tranexamic acid group (2.0 hours compared to 12.0 hours), while in the FAST-1 study (JE049 #2103) comparing icatibant with placebo, the median time to onset of symptom relief was shorter with icatibant than placebo (2.5 hours compared to 4.6 hours) but a statistically significant difference was not achieved.

Additional analyses were carried out with regard to changes from baseline to 4 hours and 12 hours in VAS scores. These direct evaluations of the VAS represent a more accurate clinical picture of the course of the HAE attack. The results show that for both studies, there was a substantial and consistent reduction in the score at 4 hours and 12 hours post-dose in the icatibant groups compared to the comparator groups, and the treatment differences in VAS changes from baseline to 4 hours and 12 hours were statistically significant ($p=0.002$ and $p=0.046$ for 4 hours and 12 hours in study JE049 #2103 and $p<0.001$ for 4 hours and 12 hours in study JE049 #2102).

Table 5 shows the results for the two pivotal trials.

Table 5: Controlled Clinical Study of Icatibant vs Tranexamic acid or Placebo: Efficacy Results

Study JE049 #2102			**Study JE049 #2103**		
	Icatibant	**Tranexamic Acid**		**Icatibant**	**Placebo**
Number of Subjects in ITT Population	36	38	Number of Subjects in ITT Population	27	29
Baseline VAS (mm)	63.7	61.5	Baseline VAS (mm)	69.3	67.7
Change from Baseline to 4 hours	-41.6	-14.6	Change from Baseline to 4 hours	-44.6	-23.5

Study JE049 #2102			Study JE049 #2103		
	Icatibant	**Tranexamic Acid**		**Icatibant**	**Placebo**
Difference Between Treatments (95% CI, p-value)	-27.8 (-39.4, -16.2) p<0.001		Difference Between Treatments (95% CI, p-value)	-22.3 (-36.1, -9.3) p=0.002	
Change from Baseline to 12 hours	-54.0	-30.3	Change from Baseline to 12 hours	-53.9	-41.0
Difference Between Treatments (95% CI, p-value)	-24.1 (-33.6, -14.6) p<0.001		Difference Between Treatments (95% CI, p-value)	-14.0 (-27.7, -0.3) p=0.046	
Median Time to Onset of Symptom Relief (h)			**Median Time to Onset of Symptom Relief (h)**		
All episodes (N = 74)	2.0	12.0	All episodes (N = 56)	2.5	4.6
Response Rate (%, CI) at 4 hr After Start of Treatment			**Response Rate (%, CI) at 4 hr After Start of Treatment**		
All episodes (N = 74)	80.0 (63.1, 91.6)	30.6 (16.3, 48.1)	All episodes (N = 56)	66.7 (46.0, 83.5)	46.4 (27.5, 66.1)
Median Time to Onset of Symptom Relief			**Median Time to Onset of Symptom Relief**		
All symptoms (h):			All symptoms (h):		
Abdominal pain	1.6	3.5	Abdominal pain	2.0	3.3
Skin swelling	2.6	18.1	Skin swelling	3.1	10.2
Skin pain	1.5	12.0	Skin pain	1.6	9.0
Median Time to Almost Complete Symptom Relief (h)			**Median Time to Almost Complete Symptom Relief (h)**		
All episodes (N = 74)	10.0	51.0	All episodes (N = 56)	8.5	23.3
Median Time to Regression of Symptoms, by Patient (h)			**Median Time to Regression of Symptoms, by Patient (h)**		
All episodes (N = 74)	0.8	7.9	All episodes (N = 56)	0.8	16.9
Median Time to Overall Patient Improvement, by Physician (h)			**Median Time to Overall Patient Improvement, by Physician (h)**		
All episodes (N = 74)	1.5	6.9	All episodes (N = 56)	10	5.7

One hundred and twenty-six patients were treated in the OLE phase for a total of 714 separate attacks. Efficacy results, available for the first 118 patients showed similar efficacy to those seen in the controlled phase of the studies. In the OLE phase, up to three doses of icatibant were permitted. The majority of attacks (89.3% and 90.9%, respectively) in both studies required only a single dose of icatibant. Thirty patients required two doses and five patients required three doses.

A total of 36 patients were treated for a total of 61 attacks of HAE affecting the larynx. The results were again similar to patients with non-laryngeal attacks of HAE with a median time to start of regression of symptoms of 0.6-1.0 hours (controlled phase).

Paediatric Population

An open-label, non-randomised single-arm study (HGT-FIR-086) 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 6 months. Eleven patients were of pre-pubertal status and 21 patients were either pubertal or post-pubertal.

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.

The primary efficacy endpoint was the time to onset of symptom relief 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 6 shows the efficacy results for HGT-FIR-086.

Table 6: Efficacy Results for HGT-FIR-086

Parameter	Pre-pubertal (n=11)	Pubertal/Post-pubertal (n=11)	Overall (n=22)
Median time to onset of symptom relief (h)	1.0	1.0	1.0
95% CI for median time (h)	1.0, 2.0	1.0, 2.0	1.0, 1.1
Minimum, Maximum time to onset of symptom relief (h)	1.0, 3.9	0.8, 2.0	0.8, 3.9

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% CI: 1.0-2.0 hours).

5.2 Pharmacokinetic Properties

The pharmacokinetics of icatibant has been extensively characterised by studies using both intravenous and subcutaneous administration to healthy volunteers and patients. The pharmacokinetic profile of icatibant in patients with HAE is similar to that in healthy volunteers.

Absorption

Following subcutaneous administration, the absolute bioavailability of icatibant is 97%. The time to maximum concentration (t_{max}) is approximately 0.5 hours.

Distribution

Icatibant volume of distribution (V_{ss}) is about 20-25 L. Plasma protein binding is 44%.

Metabolism

Icatibant is extensively metabolised by proteolytic enzymes to inactive metabolites that are primarily excreted in the urine.

In vitro studies have confirmed that icatibant is not degraded by oxidative metabolic pathways and 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

Icatibant is mainly eliminated by metabolism with less than 10% of the dose eliminated in the urine as unchanged drug. Clearance is about 15-20 L/h and independent of dose. The terminal half-life ($t_{½}$) is about 1-2 hours.

Special Populations

Data suggest an age-related decline in clearance resulting in about 50-60% higher exposure in the elderly (75-80 years) compared to patients aged 40 years. Data suggest that gender and weight do not have a significant influence on icatibant pharmacokinetics.

The pharmacokinetics of icatibant were characterised in paediatric HAE patients in Study HGT-FIR-086. Following subcutaneous administration, the t_{max} is approximately 0.5 hours and the $t_{½}$ is about 2 hours. There are no observed differences in the exposure to icatibant between HAE patients with and without an attack. Population pharmacokinetic modelling using both adult and paediatric data showed that the exposure to icatibant in the paediatric HAE population following a single subcutaneous 0.4 mg/kg administration is lower than in adult HAE patients. Despite lower exposure, the 0.4 mg/kg subcutaneous dose of icatibant in paediatric patients was sufficient to produce a clinically meaningful treatment response; in all patients, symptoms were either mild or absent within 6 hours of icatibant administration.

Limited data suggest that icatibant exposure is not influenced by hepatic or renal impairment. The influence of race on icatibant pharmacokinetics has not been evaluated.

5.3 Preclinical Safety Data

Genotoxicity

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

Carcinogenicity

In a 2 year study to evaluate the carcinogenic potential of icatibant in rats, daily subcutaneous doses up to 6 mg/kg/day (11-fold the anticipated clinical exposure in patients administered 240 mg icatibant per month, based on monthly AUC) had no effect on the incidence or morphology of tumours. Results do not indicate a carcinogenic potential for icatibant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

- Sodium chloride
- Glacial acetic acid
- Sodium hydroxide
- Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

24 months.

6.4 Special Precautions for Storage

Store below 25°C. Do not freeze.

6.5 Nature and Contents of Container

Icatibant Lupin is supplied as 30 mg icatibant (as acetate) in 3 mL in one pre-filled syringe (Type-I clear glass) with plunger stopper (bromobutyl-coated with fluorocarbon polymer). A hypodermic needle (25 G; 16 mm) is included in the package.

Pack size of one pre-filled syringe with one needle for single use in one patient.

The following equipment is required to extract and administer the appropriate dose when the prescribed dose is less than 30 mg (3 mL):

- adapter;
- 3 mL graduated syringe.

6.6 Special Precautions for Disposal

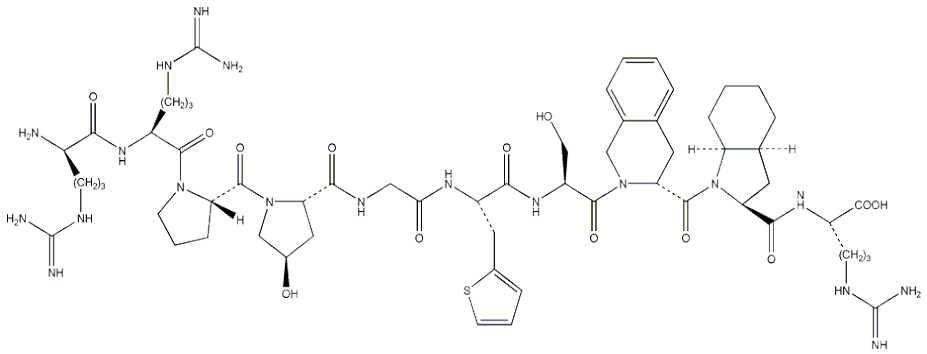
The pre-filled icatibant syringe and all other components are for single use only. All needles and syringes should be disposed of in a sharps container.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical Properties

Icatibant is isolated as the acetate salt, containing approximately 1-4 equivalents of acetic acid.

<u>Chemical Structure</u>



Chemical Name: D-Arginyl-L-arginyl-L-prolyl-L[(4R)-4-hydroxyprolyl]-glycylL[3-(2-thienyl)alanyl]-L-seryl-D-(1,2,3,4-tetrahydroisoquinolin-3-ylcarbonyl)-L[(3aS,7aS)octahydroindol-2-ylcarbonyl]-L-arginine

Molecular Formula: $C_{59}H_{89}N_{19}O_{13}S$

Molecular Weight: 1304.55

CAS Number

130308-48-4

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Lupin NZ Limited
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Level 4, Building A, BDO Centre
4 Graham Street
Auckland, 1010
New Zealand

Phone: +6498896972

9 DATE OF FIRST APPROVAL

4 September 2025

10 DATE OF REVISION

Not applicable.