FIRAZYR®

PRODUCT INFORMATION

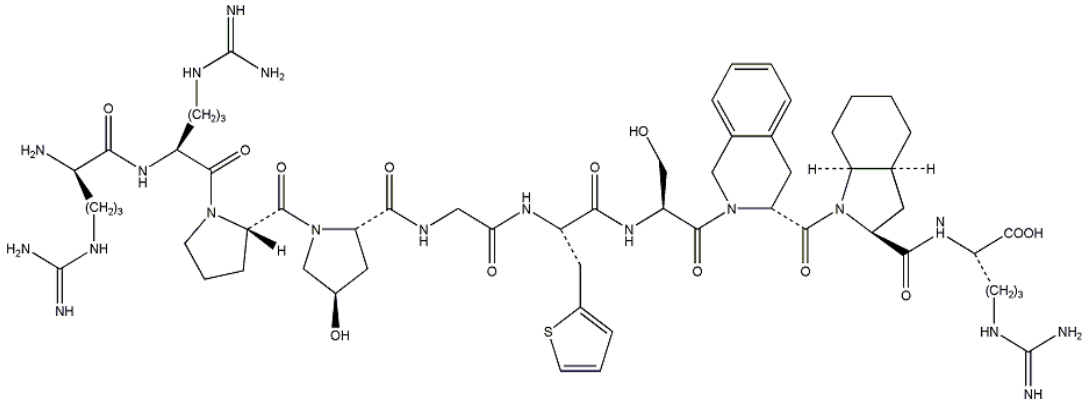
NAME OF THE MEDICINE

Icatibant acetate

Chemical Name of icatibant**:** 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)-octahydroindol-2-ylcarbonyl]-L-arginine.

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

Chemical structure of icatibant:



CAS number of icatibant**:** 130308-48-4
Chemical formula of icatibant: $C_{59}H_{89}N_{19}O_{13}S$
Molecular weight of icatibant: 1304.55
Pharmacotherapeutic group: Drugs used to treat hereditary angioedema ATC Code: B06AC02

DESCRIPTION

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.

FIRAZYR (icatibant acetate) is supplied as sterile solution for injection in single use pre-filled syringes. The solution is clear and colourless. Each 3 mL pre-filled syringe contains icatibant acetate equivalent to 30 mg icatibant. Each mL of the solution contains 10 mg of icatibant.

FIRAZYR contains the following excipients: acetic acid glacial, sodium hydroxide, sodium chloride and water for injections. The pH of the injection is approximately 5.5.

PHARMACOLOGY

Pharmacodynamic properties

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 the clinical symptoms.

HAE manifests as intermittent attacks of subcutaneous and/or sub mucosal 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 B2 receptor. In HAE increased bradykinin concentrations are the key mediator in the development of the clinical symptoms.

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.

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 is approximately 0.5 hours.

Distribution

Icatibant volume of distribution (Vss) is about 20-25 L. Plasma protein binding is 44%.

Elimination

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 is about 1-2 hours.

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.

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 a patient aged 40 years. Data

suggest that gender and weight do not have a significant influence on icatibant pharmacokinetics.

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. There are no pharmacokinetic data in children.

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 ≥20mm if the baseline VAS was 30-50mm or ≥30mm if the baseline VAS was >50mm. 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 1 shows the results for the two pivotal trials.

Table 1: Controlled Clinical Study of FIRAZYR vs Tranexamic acid or Placebo:
Efficacy Results

Study JE049 #2102			**Study JE049 #2103**		
	Icatibant	Tranex-amic 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

Table 1 cont'd: Controlled Clinical Study of FIRAZYR vs Tranexamic acid or Placebo:
Efficacy Results

Study 2102			**Study 2103**		
	Icatibant	Tranex-amic 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 (hr)			Median time to onset of symptom relief (hr)		
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: all symptoms (hr):			Median time to onset of symptom relief: all symptoms (hr):		
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 (hr)			Median time to almost complete symptom relief (hr)		
All episodes (N = 74)	10.0	51.0	All episodes (N = 56)	8.5	23.3
Median time to regression of symptoms, by patient (hr)			Median time to regression of symptoms, by patient (hr)		
All episodes (N = 74)	0.8	7.9	All episodes (N = 56)	0.8	16.9
Median time to overall patient improvement, by physician (hr)			Median time to overall patient improvement, by physician (hr)		
All episodes (N = 74)	1.5	6.9	All episodes (N = 56)	1.0	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).

INDICATIONS

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

CONTRAINDICATIONS

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

PRECAUTIONS

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 FIRAZYR 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.

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) SC 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 SC 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 SC 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 SC 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 SC (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 fetal 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 fetal 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, FIRAZYR should be used during pregnancy only if the potential benefit justifies the potential risk for the fetus (e.g. 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 FIRAZYR 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.

Paediatric Use
There is no experience of icatibant use in children.

In immature animals repeated dosing of icatibant reversibly delayed sexual maturation in males and females (See section Effects on fertility).

Use in the elderly
Limited information is available on patients older than 65 years of age. Elderly patients have been shown to have increased systemic exposure to icatibant. The relevance of this to the safety of FIRAZYR is unknown (see section Pharmacokinetic properties).

Carcinogenicity
In a 2 year study to evaluate the carcinogenic potential of icatibant in rats, daily SC 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.

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

Effects on ability to drive and use machines
FIRAZYR has minor or moderate influence on the ability to drive and use machines. Fatigue, lethargy, tiredness, somnolence, and dizziness have been reported uncommonly following the use of FIRAZYR. These symptoms may occur as a result of an attack of HAE. However, a causal relationship to the use of FIRAZYR cannot be excluded. Patients should be advised not to drive and use machines if they feel tired or dizzy.

INTERACTIONS WITH OTHER MEDICINES

Pharmacokinetic drug interactions involving CYP450 are not expected (see section Pharmacokinetic properties).

Co-administration of FIRAZYR 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.

ADVERSE EFFECTS

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 FIRAZYR 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 FIRAZYR

	Adverse reactions		
	Very common	**Common**	**Uncommon**
Gastrointestinal disorders			Nausea, vomiting
General disorders and administration site conditions	Injections site reactions (such as skin irritation, swelling, pain, itchiness, erythema, burning sensation)		Asthenia, fatigue, pyrexia
Infections and infestations			Herpes zoster, pharyngitis
Injury, poisoning and procedural complications			Contusion
Investigations		Blood creatinine phosphokinase increased, prothrombin time prolonged	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

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 FIRAZYR, 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	**FIRAZYR (%)** 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
Inection 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 FIRAZYR.

DOSAGE AND ADMINISTRATION

FIRAZYR is intended for subcutaneous injection. It contains no antimicrobial agent and should be used immediately. FIRAZYR is for single use in one patient only. Any residue should be discarded.

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

FIRAZYR is intended for use under the guidance and supervision of a doctor. Patients may self inject FIRAZYR if their doctor determines, following adequate training of the patient, that it is appropriate. 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 FIRAZYR following self-injection.

The recommended dose of FIRAZYR is one subcutaneous injection of 30 mg preferably in the abdominal area, for the treatment of a HAE attack. Injection should be given slowly due to the large volume to be administered (3 mL).

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

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

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

Hepatic impairment
No dosage adjustment is required in patients with hepatic impairment.

Renal impairment
No dosage adjustment is required in patients with renal impairment.

OVERDOSAGE

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

In case of overdose, immediately contact the Poisons Information Centre (telephone 13 11 26).

PRESENTATION AND STORAGE CONDITIONS

FIRAZYR is supplied as 30 mg icatibant (as acetate) in 3 mL in one pre-filled syringe (type I glass) with plunger stopper (bromobutyl coated with fluorocarbon polymer). Solution is clear and colourless and free from visible particles. A hypodermic needle (25 G; 16 mm) is included in the package.

Store FIRAZYR below 25°C. Do not freeze.

List of excipients:
Sodium chloride
Acetic acid, glacial (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

NAME AND ADDRESS OF THE SPONSOR

Shire Australia Pty. Limited
Level 6
123 Epping Rd
North Ryde NSW 2113
Australia

POISONS SCHEDULE OF THE MEDICINE

S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG)

7 June 2010

DATE OF MOST RECENT AMENDMENT

7 September 2016