Docusign Envelope ID: 23C77423-97B3-8BE0-8042-974CA9B18840

FIRAZYR APPROVED PACKAGE INSERT

PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

FIRAZYR 30 mg solution for injection in 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.

3. PHARMACEUTICAL FORM

Solution for injection.

The solution is a clear and colourless liquid.

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4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Firazyr is indicated for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults, adolescents and children aged 2 years and older.

4.2 Posology and method of administration

Firazyr is intended for use under the guidance of a healthcare professional.

Posology

Adults

The recommended dose for adults is a single subcutaneous injection of **Firazyr** 30 mg.

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 the clinical trials, not more than 8 injections of **Firazyr** per month have been administered.

Paediatric population

The recommended dose of **Firazyr** 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

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Body Weight	**Dose (Injection Volume)**
12 kg to 25 kg	10 mg (1,0 ml)
26 kg to 40 kg	15 mg (1,5 ml)
41 kg to 50 kg	20 mg (2,0 ml)
51 kg to 65 kg	25 mg (2,5 ml)
>65 kg	30 mg (3,0 ml)

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

No dosage regimen for children aged less than 2 years or weighing less than 12 kg can be recommended as the safety and efficacy in this paediatric group has not been established.

Elderly

Limited information is available on patients older than 65 years of age.

Elderly people have been shown to have increased systemic exposure to icatibant. The relevance of this to the safety of **Firazyr** is unknown (see section 5.2).

Hepatic impairment

No dose adjustment is required in patients with hepatic impairment.

Renal impairment

No dose adjustment is required in patients with renal impairment.

Method of administration

Firazyr is intended for subcutaneous administration preferably in the abdominal area.

Firazyr solution for injection should be injected slowly due to the volume to be administered.

Each **Firazyr** syringe is intended for single use only.

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Refer to the patient information leaflet for instructions for use.

Caregiver/self-administration

The decision on initiating caregiver or self-administration of **Firazyr** should only be taken by a medical practitioner experienced in the diagnosis and treatment of hereditary angioedema (see section 4.4).

Adults

Firazyr may be self-administered or administered by a caregiver only after training in subcutaneous injection technique by a healthcare professional.

Children and adolescents aged 2-17 years

Firazyr may be administered by a caregiver only after training in subcutaneous injection technique by a healthcare professional.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Laryngeal attacks

Patients with laryngeal attacks should be managed in an appropriate medical institution after injection until the healthcare professional considers discharge to be safe.

Ischaemic heart disease

Under ischaemic conditions, a deterioration of cardiac function and a decrease in coronary blood flow could theoretically arise from antagonism of bradykinin receptor type 2. Caution should therefore be observed in the administration of **Firazyr** to patients with acute ischaemic heart disease or unstable angina pectoris (see section 5.3).

Stroke

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Although there is evidence to support a beneficial effect of B2 receptor blockade immediately following a 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.

Caregiver/self-administration

For patients who have never received **Firazyr** previously, the first treatment should be given in a medical institution or under the guidance of a healthcare professional.

In case of insufficient relief or recurrence of symptoms after self-treatment or administration by a caregiver, it is recommended that the patient or caregiver should seek medical advice. For adults, subsequent doses that may be required for the same attack should be administered within a medical institution (see section 4.2). There are no data on administering subsequent doses for the same attack in adolescents or children.

Patients experiencing a laryngeal attack should always seek medical advice and be observed in a medical institution also after having taken the injection at home.

Paediatric population

There is limited experience with treatment of more than one HAE attack with **Firazyr** in the paediatric population.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic medicine interactions involving CYP450 are not expected (see section 5.2).

Co-administration of **Firazyr** with angiotensin-converting-enzyme (ACE) inhibitors has not been studied. ACE inhibitors are contraindicated in HAE patients due to possible enhancement of bradykinin levels.

Paediatric population

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Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

For icatibant, no clinical data on exposed pregnancies are available. Animal studies showed effects on uterine implantation and parturition (see section 5.3), but the potential risk for humans is unknown.

Firazyr should be used during pregnancy only if the potential benefit justifies the potential risk for the foetus (e.g., for treatment of potentially life threatening laryngeal attacks).

Breast-feeding

Icatibant is excreted in the milk of lactating rats at concentrations similar to those in maternal blood. No 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 breast-feeding women, who wish to take **Firazyr**, should not breast-feed for 12 hours after treatment.

Fertility

In both rats and dogs, repeated use of icatibant resulted in effects on reproductive organs. Icatibant had no effect on the fertility of male mice and rats (see section 5.3). In a study of 39 healthy adult men and women treated with 30 mg 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 concentration of reproductive hormones in either females or 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 unlikely to be sustained in the clinical setting.

4.7 Effects on ability to drive and use machines

Firazyr has minor influence on the ability to drive and use machines. Fatigue, lethargy, tiredness, somnolence, and dizziness have been reported following the use of **Firazyr**. These symptoms may

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

4.8 Undesirable effects

Summary of the safety profile

In clinical studies used for registration, a total of 999 HAE attacks have been treated with 30 mg **Firazyr** administered subcutaneously by a healthcare professional. **Firazyr** 30 mg subcutaneous has been administered by a healthcare professional to 129 healthy subjects and 236 patients with HAE.

Almost all subjects who were treated with subcutaneous icatibant in clinical trials developed reactions at the site of injection (characterised by skin irritation, swelling, pain, itchiness, erythema, burning sensation). These reactions were generally mild to moderate in severity, transient, and resolved without further intervention.

Tabulated list of adverse reactions

The frequency of adverse reactions listed in Table 2 is defined using the following convention:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000).

All adverse reactions from post-marketing experience are *italicised.*

Table 2: Adverse reactions reported with icatibant

System Organ Class (incidence category)	**Preferred Term**
Nervous system disorders	
(Common, ≥1/100 to <1/10)	Dizziness Headache
Gastrointestinal disorders	
(Common, ≥1/100 to <1/10)	Nausea
Skin and subcutaneous tissue disorders	
(Common, ≥1/100 to <1/10)	Rash Erythema Pruritus
(Unknown)	*Urticaria*

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General disorders and administration site conditions (Very Common, ≥1/10) (Common, ≥1/100 to <1/10)	 Injection site reactions* Pyrexia
Investigations (Common, ≥1/100 to <1/10)	 Transaminases increased
* Injection site bruising, Injection site hematoma, Injection site burning, Injection site erythema, Injection site hypoesthesia, Injection site irritation, Injection site numbness, Injection site edema, Injection site pain, Injection site pressure sensation, Injection site pruritus, Injection site swelling, Injection site urticaria, and Injection site warmth.	

Paediatric Population

A total of 32 paediatric patients (8 children aged 2 to 11 years and 24 adolescents aged 12 to 17 years) with HAE were exposed to treatment with icatibant during clinical studies. Thirty-one patients received a single dose of icatibant and 1 patient (an adolescent) received icatibant for two HAE attacks (in total, two doses). **Firazyr** was administered by subcutaneous injection at a dose of 0,4 mg/kg based on body weight to a maximum dose of 30 mg.

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.

Description of selected adverse reactions

Immunogenicity

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

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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 providers are asked to report any suspected adverse reactions to SAHPRA via "**6.04 Adverse Drug Reactions Reporting Form**" found online under SAHPRA's publications: http://www.sahpra.org.za/Publications/Index/8.

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.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other haematological agents, drugs used to treat hereditary angioedema; ATC code: B06AC02.

Mechanism of action

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 bradykinin type 2 (B2) receptor. It is a synthetic decapeptide with a structure similar to bradykinin, but with 5 non-proteinogenic amino acids. In HAE increased bradykinin concentrations are the key mediator in the development of the clinical symptoms.

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 efficacy and safety

Efficacy data were obtained from an initial open-label Phase II study and from three controlled Phase III studies.

Phase III clinical studies (FAST-1 and FAST-2) were randomized, double-blind, controlled trials and had identical designs. A total of 130 patients were randomized to receive either a 30 mg dose of icatibant (63 patients) or comparator (either tranexamic acid - 38 or placebo - 29 patients). Subsequent

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episodes of HAE were treated in an open label extension. Patients with symptoms of laryngeal angioedema received open label treatment with icatibant. The primary efficacy endpoint was the time to onset of symptom relief using a visual analogue scale (VAS).

FAST-3 was a randomized, placebo-controlled, parallel-group study of 98 adult patients with a median age of 36 years. Patients were randomized to receive either icatibant 30 mg or placebo by subcutaneous injection. A subset of patients in this study experienced acute HAE attacks while receiving androgens, antifibrinolytic agents or CI inhibitors. The primary endpoint was time to onset of symptom relief assessed using a 3-item composite visual analog score (VAS-3) consisting of assessments of skin swelling, skin pain, and abdominal pain

In these studies, patients on icatibant had a rapid median time to onset of symptom relief (2,0; 2,5 and 2,0 hours, respectively). The treatment effect of icatibant was confirmed by secondary efficacy endpoints.

In an integrated analysis of these controlled Phase III studies, the time to onset of symptom relief and time to onset of primary symptom relief were similar regardless of age group, sex, race and weight or not the patient used androgens or antifibrinolytic medicines.

Response was also consistent across repeated attacks in the controlled Phase III trials. A total of 237 patients were treated with 1 386 doses of 30 mg icatibant for 1 278 attacks of acute HAE. 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). 92,4 % of these attacks of HAE were treated with a single dose of icatibant.

A total of 66 patients with attacks of HAE affecting the larynx were treated in these controlled Phase III clinical trials. The results were similar to patients with non-laryngeal attacks of HAE with respect to time to onset of symptom relief.

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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 (0,4mg/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 prepubertal status and 21 patients were either pubertal or postpubertal.

The efficacy population consisted of 22 patients who had been treated with icatibant (11 prepubertal and 11 pubertal/postpubertal) for HAE attack.

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 %.

Overall the median time to onset of symptom relief was 1,0 hour (95 % confidence interval, 1,0-1,1 hours). 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).

5.2 Pharmacokinetic properties

The pharmacokinetics of icatibant has been characterized 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 30 minutes.

Distribution

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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 plasma half-life is about 1-2 hours.

Biotransformation

Icatibant is extensively metabolized 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

Elderly

Data suggest an age-related decline in clearance resulting in about 50-60 % higher exposure in older people (75-80 years) compared to patients aged 40 years.

Gender

Data suggest that there is no difference in the clearance between females and males after correcting for body weight.

Hepatic and Renal Impairment

Limited data suggest that icatibant exposure is not influenced by hepatic or renal impairment.

Race

Information on individual race effect is limited. Available exposure data suggest no difference in the clearance between non-White (n=40) and White (n=132) subjects.

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Paediatric population

The pharmacokinetics of icatibant were characterized in paediatric HAE patients in study HGT-FIR-086 (see section 5.1). Following a single subcutaneous administration (0,4 mg/kg up to a maximum of 30 mg), the time to maximum concentration is approximately 30 minutes and the terminal half-life 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 clearance of icatibant is related to body weight with lower clearance values noted for lower body weights in the paediatric HAE population. Based on modelling for weight banded dosing, the predicted exposure to icatibant in the paediatric HAE population (see section 4.2) is lower than the observed exposure in studies conducted with adult HAE patients.

5.3 Preclinical safety data

Repeated-dose studies of up to 6-months duration in rats and 9-months duration in dogs have been conducted. In both rats and dogs, there was a dose-related reduction in circulating sex hormone levels and the repeated use of icatibant reversibly delayed sexual maturation.

Maximum daily exposures defined by area under the curve (AUC) at the No Observed Adverse Effect Levels (NOAEL) in the 9-month study in dog were 2,3 times the AUC in adult humans after a subcutaneous dose of 30 mg. A NOAEL was not measurable in the rat study, however, all of the findings from that study showed either completely or partially reversible effects in treated rats. Adrenal gland hypertrophy was observed at all doses tested in rats. Adrenal gland hypertrophy was seen to reverse after cessation of icatibant treatment. The clinical relevance of the adrenal gland findings is unknown.

Icatibant had no effect on the fertility of male mice (top dose 80,8 mg/kg/day) and rats (top dose 10 mg/kg/day).

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In a 2 year study to evaluate the carcinogenic potential of icatibant in rats, daily doses giving exposure levels up to approximately 2-fold that achieved after a therapeutic dose in humans had no effect on the incidence or morphology of tumours. Results do not indicate a carcinogenic potential for icatibant.

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

Icatibant was not teratogenic when administered by subcutaneous (SC) injection during early embryonic and foetal development in rat (top dose 25 mg/kg/day) and rabbit (top dose 10 mg/kg/day). 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 foetal distress and perinatal death at high doses (10 mg/kg/day).

A 2-week subcutaneous dose range finding study in juvenile rats identified 25 mg/kg/day as a maximally tolerated dose. In the pivotal juvenile toxicity study in which sexually immature rats were treated daily with 3 mg/kg/day for 7 weeks, atrophy of testes and epididymides were observed; the observed microscopic findings were partially reversible. Similar effects of icatibant on reproductive tissue were seen in sexually mature rats and dogs. These tissue findings were consistent with reported effects on gonadotrophins and during the subsequent treatment-free period appear to be reversible.

Icatibant did not elicit any cardiac conduction change *in vitro* (hERG channel) 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. Icatibant has been shown to aggravate induced cardiac ischaemia in several non-clinical models, although a detrimental effect has not consistently been shown in acute ischaemia.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

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Acetic acid, glacial (for pH adjustment)

Sodium hydroxide (for pH adjustment)

Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Do not store above 25 °C.

Do not freeze.

6.5 Nature and contents of container

3 ml of solution in a 3 ml pre-filled syringe (type I glass) with plunger stopper (bromobutyl coated with fluorocarbon polymer). A hypodermic needle (25 G; 16 mm) is included in the pack.

Pack size of one pre-filled syringe with one needle or a multipack containing three pre-filled syringes with three needles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Paediatric use

The appropriate dose to be administered is based on body weight (see section 4.2).

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Where the required dose is less than 30 mg (3 ml), the following equipment is required to extract and administer the appropriate dose:

- Adapter (proximal and/or distal female luer lock connector/coupler)
- 3 ml (recommended) graduated syringe

The pre-filled icatibant syringe and all other components are for single use only.

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

All needles and syringes should be disposed of in a sharps container.

7. HOLDER OF CERTIFICATE OF REGISTRATION

TAKEDA (Pty) Ltd

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64 Montecasino Boulevard

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South Africa

Telephone number: 011 514 3000

8. REGISTRATION NUMBER(S)

550464

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 October 2022

10. DATE OF REVISION OF THE TEXT

04 August 2025