VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

Hereditary angioedema (HAE) is a rare inherited disorder characterized by recurrent attacks of swelling and pain involving tissues in the face, throat, lims, genitals or intestinal tract that could be serious. HAE attacks are accompanied by an increased release of bradykinin, which is the key mediator in the development of the symptoms .There are some known trigger factors, such as stress, injuries, surgeries or hormonal changes, but many attacks occur without a recognisable triggering factor. HAE typically presents as swelling attacks that are non-pitting, non-red and non-itching.

VI.2.2 Summary of Treatment Benefits

The main advantage of icatibant is the quick reduction of the symptoms of HAE.

The efficacy of icatibant in HAE has been shown in the clinical development programme. Together, the data from the clinical studies showed that a single injection of 30 mg of icatibant led to quick and long-lasting relief of skin, abdominal and throat attacks of acute HAE in adults. A single injection of 0.4 mg/kg (up to 30 mg) of icatibant led to similar safety and efficacy results in paediatric HAE subjects.

In addition, a clinical study was designed to mimic “real-life” conditions of self-administration, where adult patients self-administered 30 mg of sc icatibant (under the skin). In this study, icatibant produced quick and clinically important symptom relief which was similar to that seen in other studies where icatibant was administered by a healthcare provider.

Icatibant is used for treating the symptoms of hereditary angioedema (HAE) and blocks the activity of bradykinin.

A total of 237 patients were treated with 1,386 doses of 30 mg icatibant for 1,278 attacks of acute HAE. A beneficial effect was shown for icatibant with respect to time to onset of symptom relief since patients on icatibant had a faster symptom relief compared to comparator drug and placebo.

VI.2.3 Unknowns Relating to Treatment Benefits

Little information is available on the use of icatibant in pregnant or lactating women. Caution is recommended in these patients and icatibant should always be taken in accordance with the package insert.

The efficacy and safety of Firazyr in children less than 2 years of age have not been established. There is little information available on the use of icatibant in pregnant or lactating women.

VI.2.4 Summary of Safety Concerns

Table 1: Important Identified Risks

Risk	What is Known	Preventability
Reactions (skin irritation, swelling, pain, itchiness, redness, burning sensation) at injection site (Injection site reactions)	Injection site reactions including redness, swelling, burning, itching, warm sensation, and skin pain were noted in the majority of treated patients in clinical studies.	In clinical studies these reactions were generally mild to moderate in severity and resolved without further intervention

Table 2: Important Potential Risks

Risk	What is Known (Including reason why it is considered a potential risk)
Worsening of heart function in patients with ischaemic disease (Deterioration of cardiac function under ischaemic conditions due to bradykinin antagonism)	This is a theoretical risk due to the drug mechanism of action, but only in patients with severe acute ischaemia.
Partial bradykinin agonism (except for reactions at injection site)	This is also a theoretical risk due to the drug mechanism of action. However, at the doses used in normal practice, only injection site reactions as those described above are expected.
Potential induction of a specific immune response (Antigenicity manifesting as drug hypersensitivity and lack of efficacy)	This risk is low with icatibant, but it cannot be ruled out. In the clinical studies, no acute allergic reactions were reported.
Lack of effect (Lack of efficacy)	No cases of lack of effect in patients with laryngeal oedema have been seen in the clinical trials.
Medication errors	Medication errors are unintended mistakes in the prescribing, dispensing and administration of a medicine that could cause harm to a patient. The package leaflet and instructions for use are provided to help lessen the chance of medication errors from occurring.
Effect on reproductive hormone levels in pubertal/ post-pubertal children	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. No clinically significant changes in reproductive hormones were observed during clinical studies or in the post-approval setting.

Table 3: Missing Information

Risk	What is Known
Use in pregnant or breast-feeding women	There are no data on the use of icatibant in pregnant or breast-feeding women. Icatibant should be used during pregnancy only if the potential benefit compensates potential risk. It is unknown whether icatibant is transferred into human breast milk, so caution should be observed when it is administered to nursing women.

Table 3: Missing Information	
Risk	**What is Known**
In children less than 2 years of age	There are no data on the use of icatibant in children less than 2 years-old.

VI.2.5 Summary of Risk Minimisation Measures by Safety Concern

All medicines have a label which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet. The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned Post-authorisation Development Plan

Table 4: List of Studies in Post-authorisation Development Plan				
Study/Activity (including study number)	**Objectives**	**Safety Concerns/Efficacy Issue Addressed**	**Status**	**Planned Date for Submission of (Interim and) Final Results**
Icatibant Outcome Survey (IOS)	The objectives of the IOS are to monitor the safety of icatibant during long-term use by patients, with a focus on the frequency of cardiac ischaemic events, generalised reactions that might be indicative of B2 receptor agonism (eg, hypotension, mucosal swelling, bronchoconstriction, and aggravation of pain), use in children and adolescents (particularly effects on sexual maturation in pubertal adolescents), monitoring the safety and response to treatment in patients with laryngeal oedema, and hypersensitivity reactions.	Worsening of heart function in patients with ischaemic disease Partial bradykinin agonism (except for reactions at injection site) Potential induction of a specific immune response Lack of efficacy Effect on reproductive hormone levels in pubertal/ post-pubertal children Medication errors Use in pregnant or breast-feeding women To continue to monitor use in children and adolescents less than 18 years of age	Ongoing	Interim findings reported in PSURs
Clinical study HGT-	Primary objective: To	To continue to monitor	Ongoing	Final study report:

Table 4: List of Studies in Post-authorisation Development Plan				
Study/Activity (including study number)	**Objectives**	**Safety Concerns/Efficacy Issue Addressed**	**Status**	**Planned Date for Submission of (Interim and) Final Results**
FIR-086: An open-label, nonrandomized, single-arm study to assess the pharmacokinetics, tolerability, and safety of a single sc administration of icatibant in children and adolescents with hereditary angioedema.	investigate the PK, tolerability, and safety of a single sc dose of icatibant in children and adolescents with HAE during an acute HAE attack Secondary objectives: To evaluate the efficacy of a single sc dose of icatibant in children and adolescents with HAE. To evaluate levels of reproductive hormones after a single sc dose of icatibant in children and adolescents with HAE.	use in children and adolescents less than 18 years of age Effect on reproductive hormone levels in pubertal/ post-pubertal children Medication errors		Q1 2018

HAE=hereditary angioedema; IOS=Icatibant Outcome Survey; PK=pharmacokinetics; sc=subcutaneous

VI.2.6.1 Studies which are a Condition of the Marketing Authorisation.

None of the above studies are conditions of the marketing authorisation.