ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

Comment [piq-qrd1]: The Annexes are not fully in line with the latest QRD template (e.g. title pages missing etc.) http://www.emea.europa.eu/htms/human/qrd/qrdtemplate.htm.

1. NAME OF THE MEDICINAL PRODUCT

{Invented name} 30 mg solution for injection pre-filled syringe

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2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe of 3 ml contains 33. 3 mg icatibant acetate equivalent to 30 mg icatibant.
Each ml of the solution contains 10 mg of icatibant.

For a full list of excipients see section 6.1.

Comment [A2]: According to the SmPC guideline where the active substance is present in the form of salt or hydrate the strength should be expressed in terms of the active entity and not of the salt. In your case it is 30 mg.
Only in cases of established active substances where the strength is traditionally expressed in the form of salt the above can be reversed.

3. PHARMACEUTICAL FORM

Solution for injection.

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Deleted: This medicinal product contains less than 1mmol sodium (23 mg per dose i.e. essentially "sodium free").

Comment [piq-qrd3]: If the sodium contents are below the excipients guideline threshold then this section should not be completed and this statement should only be included in the PL.

Comment [A4]: The visual description of the product should be included.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

{Invented name} is indicated for symptomatic treatment of acute attacks of hereditary angioedema in adults.

4.2 Posology and method of administration

{Invented name} is intended for subcutaneous use.

Comment [piq-qrd5]: First you give information on posology and then on route of administration. Please move after dosage.

The recommended dose of {Invented name} is one subcutaneous injection of 30 mg administered, preferably in the abdominal area, for the treatment of a hereditary angioedema attack by a health care professional. {Invented name} is not for self-administration.

Comment [piq-qrd6]: Replace by: 'The recommended dose of {Invented name} is one subcutaneous injection of 30 mg administered by a healthcare professional, preferably in the abdominal area, for the treatment of a hereditary angioedema attack.'

Patients with laryngeal attacks need to be carefully managed in an appropriate medical institution after injection until the physician considers discharge to be safe.

Injection should be given slowly due to the large volume to be administered (3 ml).

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

In the clinical trials, not more than 8 injections of {Invented name} per month have been administered.

Children and adolescents
{Invented name} is not recommended for use in children below 18 years of age due to lack of clinical data.

Comment [piq-qrd7]: "…on safety and efficacy…" Please check the standard QRD template statement and clarify, as appropriate.

Elderly patients
Limited information is available on patients older than 65 years of age.
Elderly women have been shown to have increased systemic exposure to icatibant compared to younger patients. The relevance of this to the safety of is unknown (see section 5.2).

Comment [piq-qrd8]: There is something wrong. It does not read well.

Comment [A9]: Please include information about renal and hepatic impairment.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Ischemic heart disease
Under ischemic 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 {Invented name} to patients with acute ischemic heart disease or unstable angina pectoris (see section 5.3).

Stroke
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.

4.5 Interaction with other medicinal products and other forms of interaction

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

Co-administration of {Invented name} with ACE inhibitors has not been studied. ACE inhibitors are contraindicated in HAE patients due to possible enhancement of bradykinin levels.

Comment [piq-qrd10]: See comment above.

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This medicinal product contains less than 1 mmol sodium (23 mg per dose i.e. essentially "sodium free

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Comment [piq-qrd11]: ?? Spell out in full the 1st time it appears.

4.6 Pregnancy and lactation

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. {Invented name} 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).

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 breastfeeding women, who wish to take {Invented name}, should not breastfeed for 12 hours after treatment.

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In immature animals chronic use of icatibant reversibly delayed sexual maturation (see section. 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Comment [piq-qrd12]: This is not in line with info provided in the PL!

4.8 Undesirable effects

The safety of icatibant has been established in 1022 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 118 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.

The table below contains adverse reactions in patients treated in the controlled and the open label phase of the two trials classified according to frequency of occurrence. The frequencies are defined as: Very common ≥1/10, Common ≥1/100 to <1/10, Uncommon ≥1/1,000 to <1/100.

Note: Due to the low number of patients, each of the uncommon reactions has only been reported in a single patient.

	Adverse reactions		
	Very common (≥1/10)	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**
Congenital, familial and genetic disorders		Hereditary angioedema*	
Gastrointestinal disorders		Nausea, abdominal pain	Vomiting
General disorders and administration site conditions	Erythema, swelling, warm sensation, burning, itching, cutaneous pain	Asthenia	Fatigue, pyrexia
Infections and infestations			Pharyngitis
Injury, poisoning and procedural complications			Contusion
Investigations		Blood creatinine phosphokinase increased, liver function test abnormal	Weight increased, prothrombin time prolonged
Metabolism and nutrition disorders			Hyperuricaemia
Nervous system disorders		Dizziness, headache	
Renal and urinary disorders			Proteinuria
Respiratory, thoracic and mediastinal disorders		Nasal congestion	Asthma, cough
Skin and subcutaneous tissue disorders		Rash	Pruritus, erythema,
Vascular disorders			Hot flush

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

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

Comment [piq-qrd13]: If relevant, the statement from the QRD template "Within each frequency grouping, adverse reactions should be presented in order of decreasing seriousness" should be included and the information in the section reorganised accordingly - cf. QRD annotated template http://www.emea.eu.int/htms/human/qrd/qrdplt/AnnotatedTemplate-H.pdf and the "Guideline on Summary of Product Characteristics" http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/c/spcguidrev1-oct2005.pdf

Comment [piq-qrd14]: The use of the term "adverse reactions" is recommended when there is at least a possible causal relationship between the effects and the treatment. Adverse events without at least a suspected causal relationship should not be listed in the SPC - see "Guideline on Summary of Product Characteristics" http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/c/spcguidrev1-oct2005.pdf.

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Comment [piq-qrd15]: Where does this asterisk refer too?

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: [to be decided] ATC code: [not yet assigned].

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 edema 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 nonproteinogenic amino acids. 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.

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 placebo controlled and one with oral tranexamic acid as the comparator). The pivotal Phase III studies were otherwise identical in design. 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 episodes of HAE were treated in an open label extension. Patients with symptoms of laryngeal angioedema received open label treatment with icatibant.

In the Phase III trials, the primary efficacy endpoint was time to onset of symptom relief using a visual analogue scale (VAS). In both studies, patients on icatibant had a faster median time to onset of symptom relief (2.5 and 2.0 hours, respectively) compared to placebo (4.6 hours) and tranexamic acid (12.0 hours). The treatment effect of icatibant was confirmed by secondary efficacy endpoints.

The following table shows the results for the two pivotal trials

Controlled Clinical Study of {INVENTED NAME} vs Tranexamic acid/Placebo: Efficacy Results					
FAST 2			FAST 1		
	Icatibant	Tranexamic acid		Icatibant	Placebo
Number of subjects in ITT Population	36	38	Number of subjects in ITT Population	27	29
Median time to onset of symptom relief (hours)			Median time to onset of symptom relief (hours)		
All episodes (N = 74)	2.0	12.0	All episodes (N = 56)	2.5	4.6
Response rate (%, CI) at 4 hours after start of treatment			Response rate (%, CI) at 4 hours 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 (h):			Median time to onset of symptom relief: 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 (hours)			Median time to almost complete symptom relief (hours)		
All episodes (N = 74)	10.0	51.0	All episodes (N = 56)	8.5	23.3
Median time to regression of symptoms, by patient (hours)			Median time to regression of symptoms, by patient (hours)		
All episodes (N = 74)	0.8	7.9	All episodes (N = 56)	0.8	16.9
Median time to overall patient improvement, by physician (hours)			Median time to overall patient improvement, by physician (hours)		
All episodes (N = 74)	1.5	6.9	All episodes (N = 56)	1.0	5.7

One hundred and eighteen patients were treated in the open label extension (OLE) phase for a total of 597 separate attacks. The efficacy results were similar to those seen in the controlled phase of the studies. The majority of attacks (89.3% and 90.9%, respectively) in both studies required only a single dose of icatibant.

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).

Comment [A16]: If the EMA has waived or deferred a paediatric development, the information should be given using the standard statement provided by the SmPC guideline.

5.2 Pharmacokinetic properties

The pharmacokinetics of icatibant has been extensively 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 0.5 hours.

Distribution
Icatibant volume of distribution (Vss) is about 30 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 l/h and independent of dose. The terminal half-life is about 3 hours.

Metabolism
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
Icatibant pharmacokinetics is affected by both age and gender. AUC was similar in elderly males (66-75 years) and young females (19-36 years), but about 50% lower in young males (21-33 years) and about 2-fold higher in elderly females (66-82 years).

Limited data suggest that icatibant exposure is not influenced by hepatic or renal impairment. The influence of race and weight on icatibant pharmacokinetics has not been evaluated. There are no pharmacokinetic data in children.

5.3 Preclinical safety data

Repeated-dose studies of up to 3-months duration have been conducted in rat and dog. Maximum daily exposures (AUC) at the No Observed Adverse Effect Levels in the 3-month study in rat were 3.6 times and in the 4 week study in dog 9.4 times the AUC in humans after a subcutaneous dose of 30 mg.

Long-term studies to determine the carcinogenic potential of icatibant have not been conducted to date.

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

Icatibant was not teratogenic when administered by s.c. injection during early embryonic and fetal 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 fetal distress and perinatal death at high doses (10 mg/kg/day).

In immature animals chronic use of icatibant reversibly delayed sexual maturation.

Icatibant had no effect on the fertility of male mice and rats.

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 cardiac ischemia in several non-clinical models, although a detrimental effect has not consistently been shown in acute ischemia. Due to species differences in the effect of bradykinin, translation of the results obtained in animals to man is difficult.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Acetic acid, glacial (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Do not store above 25°C.
Do not freeze.

6.5 Nature and content of container

Pre-filled syringe (type I glass) with plunger stopper (bromobutyl coated with fluorocarbon polymer).

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Pack size: 1 x 30 mg (3 ml of solution filled in a 5 ml syringe)
A hypodermic needle (25 G; 16 mm) is included in the package.

6.6 Special precautions for disposal and other handling

The solution should be clear and colourless and free from visible particles. For single use.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

XXXXXXX
XXXXXXX

8. MARKETING AUTHORISATION NUMBER(S)

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Comment [piq-qrd17]: Format!! Numbering missing!

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu