EU RISK MANAGEMENT PLAN (RMP)

for

Firazyr (Icatibant acetate)

RMP Version number: 8.1

Date: 20-June-2025

[redacted]

[redacted]

EU Risk Management Plan for Firazyr® (Icatibant acetate)

RMP version to be assessed as part of this application:

RMP Version number: 8.1

Data lock point for this RMP: 24-October-2024

Date of final sign-off: 20-June-2025

Rationale for submitting an updated RMP: This risk management plan (RMP) is being updated to retain "Use in Pregnant and Lactating Women" as missing information as per Pharmacovigilance Risk Assessment Committee (PRAC) request during procedure EMEA/H/C/000899/II/0061.

Summary of significant changes in this RMP:

RMP Module:	Significant Changes:
Part I Product Overview	Not applicable.
Part II Safety Specification	
• **Module SI Epidemiology of the indication(s) and target population(s)**	Not applicable.
• **Module SII Non-clinical part of the safety specification**	Not applicable.
• **Module SIII Clinical trial exposure**	Not applicable.
• **Module SIV Populations not studied in clinical trials**	Not applicable.
• **Module SV Post-authorisation experience**	Not applicable.
• **Module SVI Additional EU requirements for the safety specification**	Not applicable.
• **Module SVII Identified and potential risks**	The below mentioned missing information has been added back to the RMP as per Pharmacovigilance Risk Assessment Committee (PRAC) recommendation during procedure EMEA/H/C/000899/II/0061. **Missing information** • Use in pregnant and lactating women
• **Module SVIII Summary of the safety concerns**	The safety concern removed in RMP version 8.0 is added back as below: **Missing information:** • Use in pregnant and lactating women

RMP Module:	Significant Changes:
Part III Pharmacovigilance plan	Not applicable
Part IV Plans for post-authorisation efficacy studies	Not applicable
Part V Risk minimisation measures	Updated to include missing information "Use in pregnant and lactating women".
Part VI Summary of the risk management plan	Updates made in line with Module VII and Module VIII.
Part VII Annexes	Annex 8 was updated to present the changes made from v8.0 to v8.1.

Other RMP versions under evaluation:

Not applicable.

Details of the currently approved RMP:

Version number: 7.0

Approved with procedure: EMEA/H/C/000899/II/0047

Date of approval (opinion date): 16-May-2019

QPPV name: Jean-Marie Heim, MD

Please note that e-signature may also be performed by [redacted] Deputy EUQPPV, on behalf of the EU QPPV (i.e., 'per procurationem').

QPPV signature: [redacted] RMP signatures are kept on file.

[redacted]

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[redacted]

List of Abbreviations

Abbreviation	Definition/Description
ACE	Angiotensin Converting Enzyme
ATC code	Anatomical Therapeutic Chemical classification system
AUC	Area Under the Curve
B2	Bradykinin 2
C1-INH	C1-esterase-inhibitor
CI	Confidence Interval
Cmax	Maximum Concentration
CHMP	Committee for Medicinal Products for Human Use
eCTD	electronic Common Technical Document
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
HAE	Hereditary Angioedema
GFR	Glomerular filtration rate
INN	International Non-proprietary Names
IOS	Icatibant outcome survey
Iv / IV	Intravenous
MAH	Marketing Authorisation Holder
mg	Milligram
LD_{50}	Median lethal dose
MRHD	Maximum Recommended Human Dose
NYHA	New York Heart Association
PBRER	Periodic Benefit-Risk Evaluation Report

[redacted]

Abbreviation	Definition/Description
pH	Potential of Hydrogen
PI	Product Information
PIP	Paediatric Investigation Plan
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
QTc	Corrected QT Interval
QPPV	Qualified Person Responsible for Pharmacovigilance (in the European Union)
RMP	Risk Management Plan
SC	Subcutaneous
SmPC	Summary of Product Characteristics

PART I: PRODUCT(S) OVERVIEW

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Icatibant acetate
Pharmacotherapeutic group(s) (ATC Code)	Other haematological agents, drugs used to treat hereditary angioedema (B06AC02)
Marketing Authorisation Holder	Takeda Pharmaceuticals International AG Ireland Branch
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Firazyr
Marketing authorisation procedure	Centralised procedure
Brief description of the product	Chemical class: Icatibant is a selective competitive antagonist at the bradykinin 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.
	Summary of mode of action: Bradykinin has been shown to be elevated during attacks of hereditary angioedema (HAE) and is responsible for oedema formation and related clinical symptoms of swelling and pain. Icatibant prevents pharmacological actions mediated by bradykinin, such as increased vascular permeability, vasodilatation, and the contraction of nonvascular smooth muscle cells. Icatibant competitively inhibits the binding of bradykinin to the bradykinin B2 receptor. Icatibant is extensively metabolised by proteolytic enzymes to inactive metabolites that are primarily excreted in the urine, with less than 10% of the dose eliminated as unchanged drug. It is not degraded by the 2 main enzymes angiotensin converting enzyme (ACE) and neutral endopeptidase) responsible for the short half-life of bradykinin and has been used extensively as a pharmacological tool for investigating the role of kinins.
	Important information about its composition: Each pre-filled syringe of 3 ml contains icatibant acetate equivalent to 30 mg icatibant.

<table>
<tr><td></td><td>Each ml of the solution contains 10 mg of icatibant.</td></tr>
<tr><td>Hyperlink to the Product Information (PI)</td><td>Refer to eCTD Module 1.3.1 for proposed PI or latest approved PI.</td></tr>
<tr><td rowspan="2">Indication(s) in the EEA</td><td>Current: Firazyr is indicated for symptomatic treatment of acute attacks of HAE in adults, adolescents and children aged 2 years and older with C1-esterase-inhibitor deficiency (C1-INH).</td></tr>
<tr><td>Proposed: Not applicable.</td></tr>
<tr><td>Dosage in the EEA</td><td>Current: FIRAZYR is intended for use under the guidance of a healthcare professional.
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 below.
Dosage Regimen for Paediatric Patients
<table>
<tr><td>Body Weight</td><td>Dose (injection Volume)</td></tr>
<tr><td>12 kg to 25 kg</td><td>10 mg (1.0 mL)</td></tr>
<tr><td>26 kg to 40 kg</td><td>15 mg (2.5 mL)</td></tr>
<tr><td>41 kg to 50 kg</td><td>20 ml (2.0 mL)</td></tr>
<tr><td>51 kg to 65</td><td>25 mg (2.5 mL)</td></tr>
<tr><td>>65 kg</td><td>30 mg (3.0 mL)</td></tr>
</table>
In the clinical trial, not more than 1 injection of FIRAZYR per HAE attack has been administered.</td></tr>
</table>

	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. *Method of Administration* FIRAZYR is intended for SC 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. *Caregiver/self-administration* The decision on initiating caregiver or self-administration of FIRAZYR should only be taken by a physician experienced in the diagnosis and treatment of HAE. *Adults* FIRAZYR may be self-administered or administered by a caregiver only after training in SC injection technique by a healthcare professional. *Children and adolescents aged 2-17 years.* FIRAZYR may be administered by a caregiver only after training in SC injection technique by a healthcare professional.
	Proposed: Not applicable.
Pharmaceutical form(s) and strengths	Current: Firazyr 30 mg solution for injection in pre-filled syringe. 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. List of excipients: sodium chloride; acetic acid, glacial (for pH adjustment); sodium hydroxide (for pH adjustment); water for injections
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Hereditary Angioedema	
Incidence:	HAE is a rare, debilitating, autosomal dominant disorder characterized clinically by recurrent, unpredictable, and complex attacks of edema, inflammation and pain of the face, larynx, extremities, genitals, and gastrointestinal tract that is fatal in some patients. HAE is a genetic disease, therefore data on incidence is scarce, as most studies report prevalence. One study in Germany calculated annual incidence from 2016 to 2021. In 2016, the study found an overall annual incidence of 0.52 per 100,000 persons and a pediatric incidence (age less than 12) of 0.32 per 100,000 persons. In 2021, the overall annual incidence was 0.27 per 100,000 persons and a pediatric incidence of 0.29 per 100,000 persons[redacted]. A study in Finland found the incidence ranging from 0.07 per 100,000 to 0.22 per 100,000 persons over a 10-year period, with a mean incidence of 0.16 per 100,000 persons[redacted]. HAE typically presents as edematous attacks that are non-pitting, non-erythematous and non-pruritic. There is a paucity of data relating to the frequency of attacks of HAE and this is highly variable both within a patient and between patients. Attacks can occur as frequently as every week to less than one per year[redacted]. One survey conducted in Spain, Germany, and Denmark found that 21% of respondents reported having an attack at least once a week, 38% of respondents reported having an attack at least once a month, 37% of respondents reported having an attack at least once a year, and 8% of respondents reported having less than one attack a year[redacted].
Prevalence:	Because HAE is a rare condition, reliable data on the prevalence of HAE is scarce because HAE remains underrecognized and underdiagnosed around the world, with an average delay of 10 to 15 years from initial onset of HAE symptoms to a formal diagnosis. This commonly leads to misdiagnosis and medical mismanagement in people with the condition. A systematic review found 8 studies that reported HAE prevalence. Globally, the prevalence ranged from 0.13 to 1.6 cases per 100,000. In European countries, the prevalence ranged from 0.7 to 1.6 cases per 100,000. In Sweden the prevalence 1.6 per 100,000 in 2017; in Denmark, the prevalence was 1.4 per 100,000 in 2009; in Austria the prevalence was 1.6 per 100,000 in 2019; in Belarus the prevalence was 0.7 per 100,000 in 2021 [redacted]. A study in Germany reported 12-month prevalence from 2016 to 2021, with a 12-month prevalence 1.64 per 100,000 persons in 2016 and 1.99 per 100,000 persons in 2021. Among pediatric patients (age less than 12), the 12-month

Hereditary Angioedema	
	prevalence of 0.62 per 100,000 in 2016 and 0.92 per 100,000 person in 2021 [redacted]. A study in Finland found a prevalence of 2.6 per 100,000 persons in 2021[redacted]. It is important to note that all estimates of prevalence are from diagnosed cases, thus the estimates are likely underestimates of the true population prevalence. There is limited evidence on the potential of ethnic variation in prevalence rates of HAE, though country-specific data are heavily influenced by local healthcare issues affecting recognition and care for rare conditions, and thus developing countries likely have a much larger undiagnosed rate.
Demographics of the authorised target population in the indication:	**Age:** Studies suggest that 50% of HAE patients report their first symptoms by the age of seven and over 66% report they became symptomatic by the age of 13. The frequency and severity of HAE attacks may increase during puberty and adolescence. The average age of onset of symptoms has been observed to be between 4 and 11 years of age, with estimates of about one-third of subjects showing symptoms by age 5[redacted]. Furthermore, earlier onset of HAE may be associated with increased episodes[redacted]. **Gender:** There are no gender disparities, although females may have more severe disease. The prevalence of HAE is equal in men and women, given autosomal dominant transmission of C1-INH gene mutations, though data suggest women generally have more severe clinical symptoms than men. **Ethnicity:** To date, there is limited evidence of ethnic variation in prevalence rates, though country-specific data are heavily influenced by local healthcare issues affecting recognition and care for rare conditions.
The main existing treatment options:	Contemporary medical management of HAE is divided between treatment of acute attacks and short- and long-term prophylaxis to reduce both the frequency and severity of subsequent flare-ups. However, several studies have suggested that home treatment can be safe and reduce the severity and duration of attacks. Acute treatment options for HAE include: C1-inhibitor concentrate (human plasma derived): (Berinert®, Cetor®, Cinryze®) Recombinant C1-inhibitor: (rhucin®) Ruconest® Bradykinin B2 receptor antagonist: Firazyr (icatibant) Prophylactic treatments include: C1-inhibitor concentrate Androgens/Anabolic Steroids: Danocrine® (danazol)

[redacted]

Hereditary Angioedema	
	Antifibrinolytics Kallikrein-inhibitor: Lanadelumab Berotralstat Because HAE is a non-allergic form of angioedema, symptoms do not respond to treatments for allergic reactions, such as antihistamines, corticosteroids, and epinephrine. Anabolic steroids are effective in reducing attack frequency in many patients but are associated with significant side effects. Because anabolic steroids are male hormones, their side effects can be particularly severe in female patients. In addition, these drugs cannot be given to pregnant women and children.
Natural history of the indicated condition in the untreated population, including mortality and morbidity:	C1-INH deficiency in HAE patients can result in attacks of non-pruritic swellings of the skin or mucosa. Angioedema attacks may be associated with prodromal symptoms, which commonly include fatigue, rash, and muscle aches. Swelling episodes may affect the extremities, face, gastrointestinal tract, genitourinary system, or larynx [redacted]. Attacks range in severity from mild to severe and can last up to 5 or more days; most patients suffer multiple attacks per year. With gastrointestinal involvement causing nausea, vomiting, and diarrhea; abdominal attacks may even mimic an acute surgical emergency. Abdominal attacks are often associated with nausea, vomiting, and severe pain; intestinal symptoms resembling abdominal emergencies may lead to unnecessary surgery[redacted]. As reported in an international survey of HAE patients, 19% of American patients and 24% of European patients had an unnecessary surgical procedure secondary to misdiagnosis[redacted]. Laryngeal swelling can be life threatening, and these attacks primarily account for the 30-40% mortality rate described for HAE. Laryngeal edema, which may occur in 50% of patients, can cause fatal asphyxiation due to obstruction of the upper airways, and is therefore an important clinical feature of the disease[redacted]. Approximately 50% of all HAE patients will experience a laryngeal attack in their lifetime, and there is no way to predict which patients are at risk of a laryngeal attack[redacted]. The incidence of death due to untreated laryngeal attacks is 30% to 40% and the risk of death is 3-fold greater in undiagnosed versus diagnosed patients[redacted]. Hence, HAE attacks require prompt treatment, often in an emergency room[redacted]. Risk factors associated with HAE and are often triggers of acute HAE attacks include mutation of the C1-INH gene, personal or family history, use of ACE-Inhibitors, menstruation and pregnancy, use of estrogen-derived medicines, such as

[redacted]

Hereditary Angioedema	
	oral contraceptives and hormone replacement therapy, anxiety and stress, trauma to the oral cavity caused by dental procedures, puberty, and adolescence. The triggers that lead to attacks are not well understood, but attacks tend to become more frequent and/or severe at times of physiological or psychological stress. Trauma, stress, infection and menstruation and pregnancy have been identified as possible triggers of HAE attacks[redacted]. In women, menstruation and pregnancy are reported to have a major effect on disease activity. Some female patients report a definite increase in the number of attacks during their menstrual periods, pregnancy, or while breast-feeding. Various medications, such as estrogen-containing agents and angiotensin-converting enzyme inhibitors, may also induce HAE attacks. Estrogen-derived medicines, such as oral contraceptives and hormone replacement therapy, are also associated with an increase in frequency and severity of HAE attacks and alternative, non-estrogen, birth control options [redacted]. Often used to treat high blood pressure, ACE-Inhibitors have been known to increase the frequency and severity of HAE attacks. Before attacks, many patients experience prodromal symptoms that can include tingling sensations or erythema marginatum, a nonpruritic and not raised rash. Given the propensity for children to suffer from upper respiratory tract infections, as well as experience local trauma, such triggers become especially concerning in this patient population.
Important co-morbidities:	There is a wide range of co-morbidities and/or clinical conditions, that occur in patients with HAE. These comorbidities include hypertension, cancer, depression, diabetes, and infections. Population-based studies show that due to the increased incidence of chronic diseases with age, there is generally a higher prevalence of co-morbidities in elderly patients [redacted]. Depression and anxiety are prevalent comorbidities in patients with HAE[redacted]. One survey of patients with HAE in Europe found that 38% and 14% of patients had clinically meaningful anxiety and depression, respectively. In Spain, 46% of patients reported anxiety and 12% reported depression; in Germany, 39% of patients reported anxiety and 8% reported depression; in Denmark, 24% of patients reported anxiety and 10% reported depression[redacted]. The coexistence of these medical conditions and their related treatments may impact the risk, prognosis, overall clinical management and treatment in the target population [redacted].

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

Key Safety Findings	Relevance to human usage
Toxicity: - **Key issues identified from acute or repeat dose toxicity studies** Single-dose toxicity of icatibant has been investigated following IV and SC administration. In mice, the median lethal dose (LD_{50}) for icatibant was between 48.3 and 76.7 mg/kg (IV), and between 614 and 767 mg/kg (SC). In rats, the LD_{50} was between 12.3 and 19.2 mg/kg (IV) and >1,227 mg/kg (SC). In dogs, the LD_{50} was determined to be >10 mg/kg (IV bolus) or >60 mg/kg (5-hour IV infusion). The principal findings in the repeat-dose toxicity studies in rats and dogs were effects on hormone levels, reproductive organs, and sexual maturation, as described below.	The recommended dose of icatibant in human usage is 30 mg sc.
- Reproductive/developmental toxicity Reproductive: Fertility studies in male mice (up to 80.8 mg/kg/day SC for 5 weeks prior to mating and up to 30 mg/kg/day IV for 5 weeks prior to mating), showed no impact on spermatogenesis or fertility. No effect on the pituitary-testicular axis was found when specifically investigated in a toxicology study in rats (0.25 mg/animal/day SC for 28 days). Fertility has been investigated in the rat with SC doses of 0, 1, 3, and 10 mg/kg/day administered to male animals for 10 weeks and to females for 2 weeks prior to mating. There was no effect on male fertility, but there was an increase in pre-implantation loss, a process in which bradykinin is known to be involved in the rats. Delayed parturition and fetal death in rats occurred at 0.5 and 2-fold, respectively, the maximum recommended human dose (MRHD) (on an AUC basis at maternal doses of 1 and 3 mg/kg, respectively). Increased pre-implantation loss in rats occurred at 7-fold the MRHD (on an AUC basis at a maternal daily dose of 10 mg/kg). Embryofoetal development studies have been performed in rats and rabbits, and no teratogenic effects were observed in either species. Doses used in the rat study were 0, 0.25, 2.5, and	Reproductive: 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 concentrations of reproductive hormones in females and in 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 very unlikely to be sustained in the clinical setting.

[redacted]

Key Safety Findings	Relevance to human usage
25 mg/kg/day SC during the period of organogenesis, with no adverse effects seen in dams, foetuses, or offspring. The rabbits were dosed at 0, 0.1, 1, or 10 mg/kg/day SC during the period of organogenesis; 10 mg/kg/day increased intrauterine embryofoetal death rate but had no effect on foetal development or on 24-hour pup survival. The rat pre/post-natal study dosed icatibant 0, 1, 3, and 10 mg/kg/day SC did not show any marked effects on dams during gestation, but the 10 mg/kg/day dose hindered parturition, with marginal delays also at the lower doses. Some high dose dams were euthanised because of difficulties in delivering and 2 were found dead on Days 23/24. Autopsies showed that all had dead foetuses in the uterine horns. Dams that successfully littered often continued to have clinical signs of pallor and the majority of litters died on day 1 or 2 postpartum. Pups which survived this early period tended to be initially smaller but recovered weight gain in subsequent days, and no other adverse effects on their development were noted. The fertility of the F1 generation was unaffected. Bradykinin has been implicated in parturition in the rat, therefore, these findings are not unexpected. Increased pre-implantation loss in rats occurred at 7-fold the MRHD (on an AUC basis at a maternal daily dose of 10 mg/kg). The mean number of pups born per female was lower than for the controls and pup survival rate (10 mg/kg/day) was 25% between day 1 and day 4 post-partum. After day 4 post-partum, pup survival was 100%. Studies in rabbits indicated that pre-implantation loss and increased fetal deaths occurred at 13-fold greater than the MRHD (on an AUC basis at a maternal dose of 10 mg/kg). 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). Following a single SC dose (1 mg/kg) to pregnant rats, no effects were detected in the post-natal development of rat pups.	

Key Safety Findings	Relevance to human usage
As part of the paediatric investigation plan (PIP), a 7-week toxicity study was conducted in the juvenile rat to further evaluate the effect of icatibant on fertility.	
Pregnancy: High-dose icatibant exposure of pregnant rats showed effects on the uterine implantation process and subsequent uterine instability in early pregnancy, as well as tocolytic effects resulting in severely delayed parturition in the late-stage pregnancy. Both findings are consistent with the antagonism of the known effects of bradykinin in pregnancy and parturition in rats. The 10 mg/kg/day dose in rabbits increased the intrauterine embryofoetal death rate. Animal studies showed effects on uterine implantation and parturition in rats when given at doses 3- to 30-fold the anticipated clinical exposure in young women based on area under the curve (AUC).	Pregnancy: There are no adequate and well-controlled studies in pregnant women. Icatibant should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus (e.g., patients with laryngeal attacks of HAE).
Lactation: Icatibant is excreted in the milk of lactating rats at concentrations similar to those in maternal blood. No effects on the postnatal development of rat pups were detected. No systemic effects are expected after oral intake of icatibant, due to the lack of oral bioavailability of peptides.	Lactation: It is unknown whether icatibant is excreted in human breast milk. Because many drugs are excreted in milk, caution should be observed when icatibant is administered to breast feeding women. However, systemic absorption of icatibant is not expected after oral exposure.
Developmental Toxicity: In a 7-week toxicity study, juvenile rats were dosed SC on post-natal day 22 with vehicle or icatibant at 3, 9, or 25 mg/kg/day for 7 weeks during which the animals became sexually mature. In the 9 and 25 mg/kg/day males, there were statistically significant delays in physical maturation, as well as lowered prostate and testes weights. Gross observations of small testes and epididymides were seen at 25 mg/kg/day and microscopically, tubular cell vacuolation and germ cell degeneration were seen in the testes at all doses. Decreased sperm count, motility, and velocity were observed at 25 mg/kg/day. Consequently, decreased fertility was observed in untreated females paired with icatibant dosed males (25 mg/kg/day). All microscopic and organ weight findings were either completely or partially reversible.	Developmental Toxicity: No clinically significant changes in reproductive hormones were observed during clinical studies in adults, adolescents and children aged >2 years.

Key Safety Findings	Relevance to human usage
In females, there was reduced uterine weight at SC dose levels of 9 and 25 mg/kg/day. This finding is expected, based on similar findings in previous adult rat studies. The no observed adverse effect level for females in this 7-week juvenile toxicity/ fertility study was 9 mg/kg/day. Due to the microscopic findings in the testes and epididymides seen at all dose levels, which were partially reversible after the 4-week dose-free period (including increased tubular atrophy seen after the dose-free period), a NOEL for males could not be established for this study. The findings in males at a dose level of 3 mg/kg/day represent the start of a continuum of effects seen with increasing frequency and severity with increasing dose, and the significance of these findings cannot be fully discerned from this study. The effects seen in males are largely expected due to the known effects of icatibant, a bradykinin B2 receptor antagonist. Similar effects were noted at SC doses of 3 and 9 mg/kg/day in the 26-week rat toxicity study; furthermore, these effects did not result in a functional deficit in terms of the mating performance and fertility of the male rat. Subcutaneous icatibant administration to immature dogs for 13 weeks induced a hormone imbalance in male and female dogs, which secondarily induced sexual immaturity. These effects were more marked when icatibant was administered daily at 3 or 10 mg/kg/day than when given twice weekly at 3.3 mg/kg TID, where no testicular immaturity was found in males. The effects were reversible after the cessation of treatment.	
- Genotoxicity Icatibant was found to be non-mutagenic (Ame's test) and negative for induction of chromosome aberration, both with and without metabolism activation. Subcutaneously administered icatibant was also negative within in vivo evaluations, including a chromosome aberration test in bone marrow cells of the Chinese hamster, and in micronucleus assays in the mouse and rat.	Genotoxicity assessments (in vitro and in vivo) of icatibant did not show any indication of genotoxic potential.
- Carcinogenicity The objective of the carcinogenicity studies was to determine the effects of icatibant (2, 5, or 15 mg/kg/day, twice weekly, in mice, and 1, 3, or 6 mg/kg/day, daily, in rats) on the incidence and morphology of tumours following SC administration for 104 weeks. Exposure to icatibant, and its M1 and M2 metabolites, were observed in both studies.	Not applicable.

Key Safety Findings	Relevance to human usage
Mean testosterone concentrations for treated males were lower than group mean controls in both mice and rats. This was anticipated based on the known pharmacological effect of icatibant. Icatibant related non-neoplastic findings were present at the injection sites in both studies. Importantly, there was no evidence of carcinogenic activity in either gender in mice or rats following 2-years SC icatibant administration. Lifetime carcinogenicity studies with SC icatibant in mice and rats showed no effect of icatibant on the incidence or morphology of tumours to indicate any carcinogenic potential of icatibant.	
Safety pharmacology: Safety concerns due to bradykinin antagonism: Bradykinin has been characterised experimentally as a tissue hormone with cardioprotective, antiproliferative, antihypertrophic, and antihypertensive effects. Therefore, it is possible that bradykinin antagonists can pose a potential risk to patients with cardiovascular diseases. Icatibant has been used to investigate the role of bradykinin in the heart in vitro and in vivo. Role of bradykinin and icatibant in cardiac ischaemia: The beneficial effects of bradykinin during cardiac ischaemia, attenuation of arrhythmias or improvement in cardiodynamics and metabolic state in the reperfusion phase of isolated working rat hearts, were antagonised by icatibant in a concentration-dependent fashion. The beneficial effects were restored by increasing the concentration of bradykinin. The role of bradykinin was further studied in anesthetised dogs after occlusion of a coronary artery. Early deaths (<20 minutes after occlusion) due to ventricular fibrillation were seen in both icatibant and vehicle (intracoronary infusion) treated groups, whereas late deaths (210 minutes to 320 minutes after occlusion) occurred only in the icatibant group, probably due to acute left ventricular failure. Apart from acute pump failure in the ischaemic group, icatibant induced only mild or moderate hemodynamic changes in both the ischaemic and the nonischaemic group. It was concluded that the excess mortality rate in the icatibant group was exclusively due to a highly	Safety concerns due to bradykinin antagonism: The possibility that icatibant could cause ischaemia is very unlikely, as there are many other mechanisms to regulate the blood flow other than bradykinin. In case of an acute cardiac ischaemia, e.g., acute coronary syndrome, bradykinin release is rapidly increased and could have a cardioprotective effect. Therefore, in patients with acute cardiac ischaemia a deterioration of cardiac function under icatibant is theoretically possible. In preregistration clinical trials, evidence of severe symptomatic coronary artery disease or congestive heart failure New York Heart Association (NYHA) Class III and IV were exclusion criteria. No cardiovascular safety concerns were observed in pre-registration clinical trials. The potential risk to humans lies in the use of icatibant in the presence of acute myocardial ischaemia. Such use is unlikely given the clinical situation. There is no evidence that antagonism of the B2 receptor can induce myocardial ischaemia in its own right. The cases received to date do not change the risk assessment and no update to the Summary of Product Characteristics (SmPC) is recommended. No relevant influence on blood pressure or ischaemia-induced arrhythmias is

Key Safety Findings	Relevance to human usage
effective blockade of endogenously generated kinins by the intracoronary administration of icatibant. Effects of icatibant on ischaemia-induced arrhythmias revealed different result in rats and in dogs: Whereas icatibant was protective in rats exposed to ischaemic myocardial preconditioning, this was not the case in dogs. This may be explained by partially bradykinin preconditioning, this was not the case in dogs. This may be explained by partially bradykinin agonistic effects in rats, whereas purely bradykinin antagonistic effects in dogs may be the explanation. Icatibant has no intrinsic hypertensive effect of its own, as demonstrated in normotensive and hypertensive animal models as well as in healthy human volunteers and Phase II studies in patients with liver cirrhosis, asthma, allergic rhinitis, or postoperative pain. Safety concerns due to effect on mast cells and partial bradykinin agonism: Mediator release: Icatibant at concentrations up to 100 µM did not release histamine from rat peritoneal mast cells and inhibited the bradykinin-induced release of histamine. In contrast, in vitro tests on human mast cells showed that icatibant activated human cutaneous mast cells. This activation occurred within minutes and comprised release of histamine and tryptase, as well as de novo synthesis of leukotrienes, prostaglandins, and cytokines. High concentrations of icatibant can also stimulate the release of calcitonin gene-related peptide in mouse skin independently of mast cell activation, but dependent on the expression of B2 receptors. Generalised reactions, e.g., hypotension: Icatibant at doses of 0.6 and 1 mg/kg in conscious beagle dogs markedly decreased blood pressure for 5 to 10 minutes when given as a 1minute IV bolus. Concomitant symptoms were pain reaction, restlessness, mydriasis, and hypersalivation. By contrast, an SC dose as high as 13 mg/kg did not decrease blood pressure, although it has been demonstrated in several models that the SC efficacy of icatibant against exogenously applied bradykinin and endogenously generated kinins is about equal to the IV route and lasts for several hours. Thus, the peak concentration achieved during IV bolus injections of high doses of icatibant appears to be a	expected and has not been reported during post-marketing use. Injection site reactions: In clinical trials with 30 mg SC icatibant (adults) or 0.4 mg/kg up to 30 mg in paediatric population, injection site reactions (characterised by skin irritation, swelling, pain, itchiness, erythema, burning sensation) immediately after administration were seen in most subjects. Erythema was noted in almost all cases, whereas other symptoms such as pain were reported less frequently. However, these symptoms are usually mild to moderate in severity and resolve spontaneously within a few hours. Data from preclinical studies implicate icatibant induced mast cell activation, release of neuropeptides from peripheral nerves, and partial agonism as mechanisms underlying the injection site reactions in man. Systemic effects: In a Phase I trial (JE049 #1001) it was demonstrated that at high doses (3.2 mg/kg infusion over 1 hour) of icatibant, mild orthostatic hypotension, erythema and itching occurred; whereas, at the lower doses only bradykinin antagonistic effects like a dose- and time-dependent inhibition of hypotension or reflex tachycardia elicited by a preselected bradykinin challenge dose were seen. These results suggest that, whereas at lower doses icatibant only works as potent bradykinin antagonist, at higher doses, a partial agonistic activity of icatibant is possible. The partial bradykinin agonistic effects only were seen when administered as iv bolus at doses approximately 8 times the therapeutic dose and resolved without therapeutic intervention. Therefore, at the currently proposed dose, no systemic bradykinin agonistic effects are expected.

[redacted]

Key Safety Findings	Relevance to human usage
key factor for a hypotensive effect; this phenomenon could be due to partial agonistic activity of icatibant on endothelium, involving release of nitric oxide and prostacyclin in response to bradykinin, as well as liberation of histamine from mast cells. While the beneficial effects of bradykinin in the ischaemic heart were clearly antagonised at lower doses of icatibant, attenuation of arrhythmias was observed at a concentration of 10 nM in isolated working rat hearts, suggesting a bradykinin agonistic effect at those concentrations. In animal trials using high dose bolus IV administration of icatibant, oedema of lips was observed, which was considered to be probably due to partial bradykinin agonism and/or mediator release from mast cells. Distinct species differences probably exist in the effect of bradykinin, in the distribution of its receptors, and in the concentration threshold of icatibant at which an agonistic effect may overlap the antagonistic activity. This makes translation of the results obtained in animals to man difficult.	In case of an overdose with icatibant, mild transient reactions such as hypotension, swelling of mucous membranes, erythema, itching, bronchoconstriction, or aggravation of pain are possible; however, these are not expected with the current SC formulation.
<u>Nervous system</u> Not conducted.	Not applicable.
<u>Nephrotoxicity:</u> Renal toxicity was seen in the rat, both histologically (areas of epithelial necrosis, areas of repair, and foci of tubular atrophy) and biochemically (raised blood urea nitrogen and serum creatinine) during 4-week studies at a dose level of 10 mg/kg, administered IV or SC. These effects were restricted to studies in 1 sub strain of rats and no effects on the kidney were seen in subsequent studies in the rat that were of longer duration or at higher doses. No renal toxicity has been observed in the dog, even up to a dose of 30 mg/kg iv (4-week study).	Clinical trial JE049 #1001 was especially designed to investigate any potential renal toxicity following single and multiple iv infusion in 26 healthy male subjects between 19 and 39 years of age. No adverse effects were seen. No changes were observed in renal function (GFR), renal plasma flow, proximal tubular function, electrolyte excretion, or hormonal profiles (plasma renin activity, endothelin-1, and aldosterone). In patients with hepatorenal syndrome (GFR 30-60 mL/min) in trial JE049 #2002 receiving icatibant 0.15 to 1.2 mg/kg/24 hours IV over 5 days, no relevant changes in the clearance of icatibant were noted. Given the clinical data to date, renal toxicity is not considered to be a potential risk in humans.

Key Safety Findings	Relevance to human usage
Other toxicity-related information or data: Hepatotoxicity: Mice administered icatibant by SC administration at 0, 5.0, 15, or 50 mg/kg/dose, twice weekly, for a period of 13 weeks showed non-adverse dose related findings in the liver and other organs. In the repeat-dose study conducted in the adult rat over 26-weeks at SC dose levels of 0, 3, 10, and 30 mg/kg/day, including a 4-week recovery period, small increases (up to 2.5 times control values) in liver enzymes were observed in both sexes, predominantly at 30 mg/kg/day, together with increased liver weight and histopathologically, centrilobular hypertrophy.	Hepatotoxicity: JE049-2001 was a Phase IIa study to explore the safety, tolerance, PK and PD profile of multiple doses of icatibant administered iv to patients with hepatic insufficiency. JE049-2002 was a Phase IIa study to assess the safety and tolerance of icatibant in patients with cirrhosis with refractory ascites (with or without hepatorenal syndrome), and to explore PK and metabolism in patients with severe hepatic insufficiency. JE049-2002 was a Phase IIa study to assess the safety and tolerance of icatibant in subjects with cirrhosis with refractory ascites (with or without hepatorenal syndrome), and to explore pharmacokinetics and metabolism in subjects with severe hepatic insufficiency. Systemic and local tolerance was good, without indication of labile blood pressure or orthostatic hypotension in this very sensitive population. No prolongation of QTc and no hepatic or renal toxicity were documented. Renal function (GFR) was well-preserved throughout the 5-day treatment with IV icatibant. Icatibant was used safely in subjects with mild to moderate hepatic and renal impairment. No accumulation with repeated doses occurred in these special populations.
Antigenicity: No anti-icatibant antibody formation was observed in any serum samples from animals given 2.5 mg icatibant solution, intranasal or SC. In guinea pigs sensitized with icatibant plus adjuvants, weak antibody formation was observed, but icatibant without adjuvant did not result in antibody formation. Icatibant was also evaluated for sensitizing properties in the classical Magnusson and Kligman maximisation test. In this test, 80% of the animals had a slight to well defined erythema, and no reactions were observed in the control animals. Icatibant is considered a potential sensitizer via skin contact.	Antigenicity: Potential risks from antibodies to icatibant could arise due to hypersensitivity to the drug or due to lack of efficacy because of neutralizing antibodies. Across repeated treatment in the controlled Phase III trials, transient positivity to anti-icatibant antibodies was observed in 4 cases. Three of these patients had subsequent tests that were negative. All patients-maintained efficacy. One treated patient tested positive for anti-icatibant antibodies before and after treatment with icatibant.

[redacted]

Key Safety Findings	Relevance to human usage
The conducted hyperimmunisation studies demonstrate that even icatibant-protein conjugates in combination with adjuvant did not elicit a sustained antibody response against icatibant in several relevant species. These results corroborate the extremely low immunogenic potential of icatibant and are in line with the fact that no signs of drug-related antibody responses were observed in any of the toxicity and clinical studies.	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. No association between anti-icatibant antibodies and efficacy was observed.
Mechanisms for Drug Interactions Icatibant and its metabolites M1 and M2 were tested for in vitro metabolic stability in the presence of human liver microsomes and (for icatibant only) in the presence of dog liver microsomes as well as dog and human S9-fractions. In vitro studies investigating effects on human CYP enzymes did not show any induction or inhibition. The data from these studies showed that the metabolism of icatibant, M1, and M2 is CYP-independent. ACE inhibitors, which increase bradykinin concentration by inhibition of bradykinin metabolism, show beneficial effects similar to those of bradykinin. These effects were abolished by icatibant, as shown in several in vitro and in vivo studies.	Mechanisms for Drug Interactions PK drug interactions involving CYP450 are not expected, and no interactions have been identified. In cases of patients treated with ACE inhibitors for hypertension, a single SC dose of icatibant for treatment of an acute HAE attack will only diminish efficacy of the ACE inhibitor for a restricted time period, which is not expected to be clinically relevant. In addition, ACE inhibitors may induce or exacerbate an attack of HAE, therefore patients with HAE should not use ACE inhibitors.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Table SIII.1: Duration of exposure

Exposure to icatibant in the HAE and ACE-I induced angioedema indication cumulatively through 11 -July-2024 is presented in Table 1 through Table 12 below.

Table 1: Exposure to Icatibant (All Subjects)

	HAE	ACE-I Induced Angioedema
Number of subjects exposed	398	60
Number of attacks treated	1,468	60
Number of doses administered	1,590	60

ACE-I=Angiotensin converting enzyme inhibitor, HAE=Hereditary angioedema.

Studies JE049-2101, JE049-2102, JE049-2103, HGT-FIR-054, JE049-3101, HGT-FIR-086, HGT-FIR-096, SHP-FIR-301 and TAK-667-3001.

Table 2: Exposure to Icatibant (Randomised Blinded Population Only)

	HAE	ACE-I Induced Angioedema
Number of subjects exposed	113	60
Number of attacks treated	113	60
Number of doses administered	113	60

ACE-I=Angiotensin converting enzyme inhibitor, HAE=Hereditary angioedema.

Studies JE049-2102, JE049-2103, HGT-FIR-054, HGT-FIR-096.

Exposure to icatibant by number of attacks treated is presented in Table 3 for the HAE indication and in Table 4 for the ACE-I induced angioedema indication.

Table 3: Exposure by Number of Attacks (All Subjects)

Indication: HAE

No. of attacks	No. of subjects Exposed	No. of Attacks Treated	No. of Doses Administered
0 attack	8	0	8
1 attack	189	189	197
2-5 attacks	147	406	434

Table 3: Exposure by Number of Attacks (All Subjects)			
Indication: HAE			
No. of attacks	**No. of subjects Exposed**	**No. of Attacks Treated**	**No. of Doses Administered**
6-10 attacks	26	200	216
>10 attacks	30	673	735
HAE=Hereditary angioedema Studies JE049-2101, JE049-2102, JE049-2103, HGT-FIR-054, JE049-3101, HGT-FIR-086, SHP-FIR-301 and TAK-667-3001. Only HAE subjects are included.			

Table 4: Exposure by Number of Attacks (All Subjects)		
Indication: ACE-I Induced Angioedema		
No. of Attacks	**No. of Subjects Exposed**	**No. of Doses Administered**
0 attack	0	0
1 attack	60	60
2-5 attacks	0	0
6-10 attacks	0	0
>10 attacks	0	0
ACE-I=Angiotensin converting enzyme inhibitor Study HGT-FIR-096. Only ACE-I induced angioedema subjects are included.		

Table SIII.2: Age group and gender

Exposure to icatibant by age group and sex is presented in Table 5 for the HAE indication and in Table 6 for the ACE-I induced angioedema indication.

Table 5: Exposure by Age Group and Gender (All Subjects)				
Indication: HAE				
Age Group	**Sex**	**No. of subjects exposed**	**No. attacks treated**	**No. of doses administered**
<18 years	Male	20	19	27

[redacted]

Table 5: Exposure by Age Group and Gender (All Subjects)				
Indication: HAE				
	Female	14	20	22
18-45 Years	Male	86	280	302
	Female	164	640	693
46-65 Years	Male	35	258	277
	Female	66	190	203
>65 Years	Male	4	5	5
	Female	9	56	61

HAE=Hereditary angioedema.

Studies JE049-2101, JE049-2102, JE049-2103, HGT-FIR-054, JE049-3101, HGT-FIR-086, SHP-FIR-301 and TAK-667-3001.

Only HAE subjects are included.

Table 6: Exposure by Age Group and Sex (All Subjects)			
Indication: ACE-I Induced Angioedema			
Age Group	**Sex**	**No. of Subjects exposed**	**No. of Doses Administered**
<18 Years	Male	0	0
	Female	0	0
18-45 Years	Male	5	5
	Female	2	2
46-65 Years	Male	17	17
	Female	16	16
>65 Years	Male	11	11
	Female	9	9

ACE-I=Angiotensin converting enzyme inhibitor.

Study HGT-FIR-096.

Only ACE-I induced angioedema subjects are included.

Table SIII.3: Dose

Table 7: Exposure by Dose (All Subjects)			
Indication: HAE			
Dose	**No. of Subjects Exposed**	**No. of Attacks Treated**	**No. of Doses Administered**
0.4 mg/kg IV infusion	7	8	8
0.4 mg/kg SC infusion	32	35	45
0.8 mg/kg IV infusion	4	4	4
30 mg SC injection	348	1,314	1,321
45 mg SC injection	5	5	5
60 mg (2x30 mg) SC injection	47	96	189
90 mg (3x30 mg) SC injection	6	6	18
Total	398	1,468	1,590
HAE=Hereditary angioedema; IV=Intravenous, SC=Subcutaneous. Studies JE049-2101, JE049-2102, JE049-2103, HGT-FIR-054, JE049-3101, HGT-FIR-086, SHP-FIR-301 and TAK-667-3001. Only HAE subjects are included.			

Table 8: Exposure by Dose (All Subjects)		
Indication: ACE-I Induced Angioedema		
Dose	**No. of Subjects Exposed**	**No. of Doses Administered**
0.4 mg/kg IV infusion	0	0
0.4 mg/kg SC infusion	0	0
0.8 mg/kg IV infusion	0	0
30 mg SC injection	60	60
45 mg SC injection	0	0
60 mg (2x30 mg) SC injection	0	0

[redacted]

Table 8: Exposure by Dose (All Subjects)		
Indication: ACE-I Induced Angioedema		
Dose	**No. of Subjects Exposed**	**No. of Doses Administered**
90 mg (3x30 mg) SC injection*	0	0
Total	60	60

*Per study protocols no more than 3 30mg doses per 24 hours, at least 6 hours apart, were allowed

ACE-I=Angiotensin converting enzyme inhibitor; IV=Intravenous, SC=Subcutaneous

Study HGT-FIR-096.

Only ACE-I induced angioedema subjects are included.

Exposure to icatibant by number of dose is presented in Table 9 for the HAE indication and in Table 10 for the ACE-I induced angioedema indication.

Table 9: Exposure by Number of Doses (All Subjects)	
Indication: HAE	
Number of Doses	**No. of Subjects**
Single dose	189
2 doses	73
3 doses	44
4 doses	20
5 doses	14
6 doses	10
7 doses	3
8 doses	3
9 doses	6
≥10 doses	38

HAE=Hereditary angioedema.

Studies JE049-2101, JE049-2102, JE049-2103, HGT-FIR-054, JE049-3101, HGT-FIR-086, SHP-FIR-301 and TAK-667-3001.

Only HAE subjects are included.

Table 10: Exposure by Number of Doses (All Subjects)	
Indication: ACE-I Induced Angioedema	
Number of Doses	**No. of Subjects**
Single dose	60
2 doses	0
3 doses	0
4 doses	0
5 doses	0
6 doses	0
7 doses	0
8 doses	0
9 doses	0
≥10 doses	0
ACE-I=Angiotensin converting enzyme inhibitor. Study HGT-FIR-096. Only ACE-I induced angioedema subjects are included.	

Table SIII.4: Ethnic origin

Exposure to icatibant by race is presented in Table 11 for the HAE indication and in Table 12 for the ACE-I induced angioedema indication.

Table 11: Exposure by Race (All Subjects)			
Indication: HAE			
Race	**No. of Subjects Exposed**	**No. of Attacks Treated**	**No. of Doses Administered**
White	373	1,363	1,479
Black or African American	5	31	33
Native Hawaiian or other Pacific Islander	0	0	0
Asian	11	14	14

Table 11: Exposure by Race (All Subjects)			
Indication: HAE			
American Indian or Alaska Native	0	0	0
Other	9	60	64
Total	398	1,468	1,590

HAE=Hereditary angioedema

Studies JE049-2101, JE049-2102, JE049-2103, HGT-FIR-054, JE049-3101, HGT-FIR-086, SHP-FIR-301 and TAK-667-3001.

Only HAE subjects are included.

Table 12: Exposure by Race (All Subjects)		
Indication: ACE-I Induced Angioedema		
Race	**No. of Subjects Exposed**	**No. of Doses Administered**
White	18	18
Black or African American	40	40
Native Hawaiian or other Pacific Islander	0	0
Asian	1	1
American Indian or Alaska Native	0	0
Other	1	1
Total	60	60

ACE-I=Angiotensin converting enzyme inhibitor.

Study HGT-FIR-096.

Only ACE-I induced angioedema subjects are included.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1. EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

History of any haematological, hepatic, respiratory, cardiovascular, renal, or other medical condition that is capable of altering the metabolism or elimination of drugs or may interfere with assessment of tolerability	
Reason for exclusion:	It is considered potentially unsafe for these subjects to be enrolled in clinical studies; exclusion is not specific to icatibant.
Is it considered to be included as missing information:	No.
Rationale:	These restrictions are common to most clinical studies. Such patients should be managed according to the clinical judgment of the treating physician.

Pregnancy	
Reason for exclusion:	No clinical data on exposed pregnancies are available. Animal studies showed effects on uterine implantation and parturition, but the potential risk for humans is unknown.
Is it considered to be included as missing information:	Yes
Rationale:	Icatibant 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).

Evidence of severe, symptomatic coronary artery disease, congestive heart failure NYHA class III or IV	
Reason for exclusion:	Theoretical risk of B2 receptor antagonism in the presence of acute myocardial ischaemia.
Is it considered to be included as missing information:	No

Evidence of severe, symptomatic coronary artery disease, congestive heart failure NYHA class III or IV	
Rationale:	No cardiovascular safety concerns were observed in pre-registration clinical trials. Caution should be observed in the administration of icatibant to patients with acute ischaemic heart disease or unstable angina pectoris.

Serious concomitant illnesses	
Reason for exclusion:	It is considered potentially unsafe for these subjects to be enrolled in clinical studies; exclusion is not specific to icatibant.
Is it considered to be included as missing information:	No
Rationale:	These restrictions are common to most clinical studies. Such patients should be managed according to the clinical judgment of the treating physician.

Angioedema other than HAE	
Reason for exclusion:	A diagnosis of angioedema attack other than HAE could confound the interpretation of study results.
Is it considered to be included as missing information:	No
Rationale:	Such patients should be managed according to the clinical judgment of the treating physician.

Treatment with ACE inhibitors	
Reason for exclusion:	Patients treated with ACE inhibitors may experience angioedema as a side effect. A diagnosis of angioedema attack could be due to the ACE inhibitor, and it may not be possible clinically to determine whether an attack is due

Treatment with ACE inhibitors	
	to HAE or the ACE inhibitor. This could confound the interpretation of study results.
Is it considered to be included as missing information:	No
Rationale:	Studies have shown that icatibant may be effective in treating ACE inhibitor induced angioedema [redacted]. However, results of study HGT-FIR-096 showed that there was no difference between icatibant and placebo in the treatment of angiotensin converting enzyme inhibitors (ACE-I) induced angioedema. Whether bradykinin has an important role has an important role in ACE-I-induced angioedema is not yet determined, but based on the studies conducted in this indication there is no harm in administering icatibant in this setting.

Documented history of allergy or hypersensitivity to any medication	
Reason for exclusion:	Patients with a history of hypersensitivity to icatibant or to any of its excipients should receive an alternative therapy.
Is it considered to be included as missing information:	No
Rationale:	Hypersensitivity to the active substance or to any of the excipients listed in the SmPC.

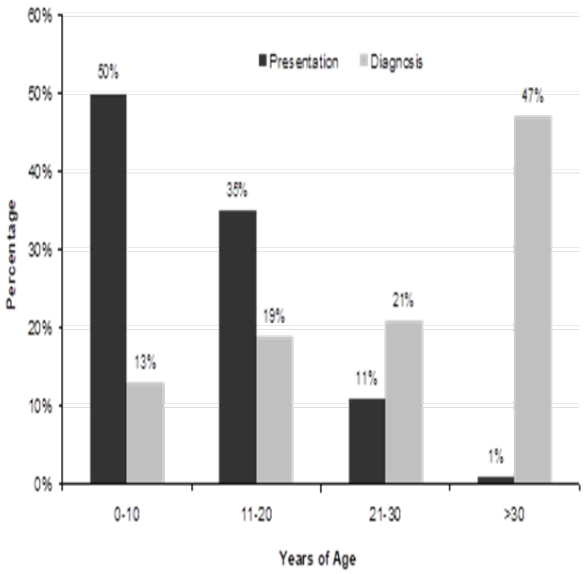
SIV.2. LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged exposure.

SIV.3. LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	
Patients with relevant comorbidities: - Patients with hepatic impairment	In trial JE049 #2001, icatibant was investigated in patients with hepatic impairment (Child-Pugh score ≥5 and ≤12) and in trial JE049 #2002 in patients with liver cirrhosis and refractory as cites (Child-Pugh score ≥7 and ≤13). No significant changes in heart rate, blood pressure, electrocardiogram parameters (including QTc interval), and laboratory safety were noted. Icatibant clearance in subjects with liver disease was similar to that obtained in healthy subjects.
Patients with renal impairment	Clearance of icatibant is predominantly renal; however, the main part is metabolised by proteolytic enzymes to 2 inactive metabolites, M1 and M2, and only <10% of icatibant is excreted unchanged. M1 and M2 are excreted unchanged. In trial JE049 #2002, icatibant was studied in subjects with hepatorenal syndrome (including 10 subjects with pre-treatment GFR between 30 and 6 mL/min randomised to 1 of the icatibant treatment groups). The subjects were dosed over a 5-day, continuous infusion of 0.15-1.2 mg/kg/day. No relevant changes in the clearance of icatibant were noted. Icatibant was safe and well tolerated in all patients. Due to the extensive metabolism to 2 inactive metabolites, the presence of renal impairment is considered unlikely to affect the safety profile of icatibant, which was supported by the abovementioned study.
Patients with a disease severity different from inclusion criteria in clinical trials	Patients on treatment with ACE inhibitors: Inhibition of degradation of bradykinin by ACE inhibitors, leading to an increased bradykinin concentration, may contribute to the antihypertensive effect of these drugs. As a bradykinin antagonist, icatibant would antagonise this effect of the ACE inhibitors. In trials JE049 #2103 and JE049 #2102, patients receiving ACE

Type of special population	Exposure
	inhibitors were excluded. However, the possibility that short-term administration of icatibant will alter significantly the chronic antihypertensive effect of an ACE inhibitor is very remote. Patients with HAE should not be using ACE inhibitors as they induce or exacerbate an attack of HAE.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Other: Children and Adolescents	HAE attacks usually commence in the first decade of life, although they are frequently not recognised at that stage (Figure 1). However, attacks in prepubescent children are usually infrequent, less severe, and are predominantly abdominal. Most attacks can be managed with pain relief and anti-emetics, although some attacks even in this young age cohort may necessitate more specific intervention. Attacks in postpubescent children can be more severe and off-label use in those cases is expected.  Source: Agostoni A and Cicardi M The pre-requisite studies included in the PIP endorsed by the European Medicines Agency/Paediatric Committee (EMA/PDCO) are summarised below: • A SC administration local tolerance study in juvenile rats and a 7-week toxicity study in juvenile rats with assessment of fertility before

Type of special population	Exposure
	and after recovery. Results are summarised in Module SII (Juvenile toxicity). • A double-blind, randomized, placebo-controlled study to assess the effect of icatibant on serum reproductive hormone levels after repeated administration of 3 SC doses in healthy adult volunteers (HGT-FIR-062). A total of 39 healthy adult subjects (23 males and 16 females) with normal reproductive hormone levels were enrolled and randomised to treatment with either icatibant or placebo. Twenty subjects were treated with icatibant and 19 received placebo. Multiple administrations of icatibant were well tolerated, and the safety profile of icatibant was consistent with that observed in other clinical studies. Repeated doses of icatibant had no clinically concerning effect on basal or stimulated levels of circulating reproductive hormones or on other fertility parameters in healthy male and female adult subjects in this study. ○ No clinically significant changes from baseline in basal and GnRH-stimulated concentrations of reproductive hormones were observed in subjects exposed repeatedly to icatibant. ○ Additionally, there were no significant effects of icatibant on semen parameters in males, and there were no significant effects of icatibant on the concentration of luteal phase progesterone, an indicator of ovulation status and luteal function, or on menstrual cycle length in females. • Open-label, non-randomised, single-arm study to assess the PK, tolerability, and safety of a single SC administration of icatibant in children and adolescents (aged 2 to <18 years) with HAE (HGT-FIR-086). The first phase of the study was completed. A total of 32 paediatric subjects with HAE were exposed to treatment with icatibant, 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 icatibant for 2 HAE attacks (in total, 2 doses). The majority of paediatric patients who were treated with SC icatibant developed adverse reactions at the site of injection. The reactions included erythema, swelling, burning sensation, skin pain and

Type of special population	Exposure
	itching/pruritus; these were found to be mild to moderate in severity and consistent with reactions that have been reported in adults. No clinically significant changes in reproductive hormones were observed during clinical studies. The PK of icatibant was also characterised in paediatric HAE patients in study HGT-FIR-086. Following SC administration, the time to maximum concentration (Cmax) 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 PK 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 is lower than the observed exposure in studies conducted with adult HAE patients. The second phase of the study was completed to assess the effect of icatibant in subsequent HAE attacks in 10 pubertal/post pubertal subjects either by HCP or caregiver administration. Icatibant was well tolerated across repeated exposures, and no new safety signals were identified in pediatric subjects 2 to <18 years of age. The safety profile was favorable and consistent with previous experience icatibant in adult HAE subjects. No clinically significant changes in reproductive hormones were observed. In conclusion, this study demonstrated that icatibant can address the unmet medical need for a safe and effective treatment for acute attacks of HAE in pediatric patients. The safety and efficacy of icatibant has not been established in children less than 2 years of age or weighing < 12 kg.
Elderly	In trial JE049 #1103, icatibant was used safely in the elderly male and female subjects. A difference in exposure based on age and gender has been observed: age had a significant effect on apparent clearance, which was lower (<0.6-fold) in elderly compared to young adult subjects. This was reflected by an increase in total plasma exposure of

Type of special population	Exposure
	icatibant. In elderly subjects, AUC0-∞ was significantly higher than in young subjects, by >1.6-fold for females and >2.3-fold for males. The exposure to icatibant was also markedly influenced by gender in this study. Females showed a significantly higher AUC0–∞ and Cmax compared to males with 1.6- to 2.4-fold increases for AUC0–∞ and 1.6- to 2.2-fold increases for Cmax. The highest exposure in this trial was observed in the elderly female subjects, where mean Cmax and AUC0–∞ was 2,709 ng/mL and 4,757 ng*h/mL, respectively. The lower clearance was associated with a significantly prolonged t½ in elderly (1.3 hour) compared to young adult (0.6 hour) subjects. Despite the longer t½, no relevant accumulation of icatibant is expected to occur in elderly after administration of multiple SC doses for the applied dosing intervals. Population analysis of all relevant PK data (215 treatments in 58 male and 34 female subjects) confirmed a small age effect on the PK. Gender, however, was not confirmed to be a covariate based on the population analysis of all available data. In summary, in trial JE049 #1103, elderly females had an AUC approximately 4 times that of young adult males. However, in trial JE049 #1001 in male subjects, a single dose infusion of 1.6 mg/kg iv over 1 hour that resulted in a mean Cmax and AUC0–∞ of 5,614 ng/mL and 7,402 ng*h/mL, respectively, was safe and well tolerated. In trial JE049 #2101 a dose of 0.8 mg/kg given as an IV infusion (0.5 hours) (Cmax and AUC0-∞ were 4,683 ng/mL and 5,217 ng*h/mL, respectively) also was safe and well-tolerated in HAE patients. There is a sufficient safety margin for a SC dose of 30 mg for all patient populations, including elderly female patients, for whom the highest exposure to icatibant has been shown. 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.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1. POST-AUTHORISATION EXPOSURE

SV.1.1. Method used to calculate exposure

The occurrence of HAE attacks does not follow a typical pattern, and the number and severity of attacks differ markedly between patients and within a patient from one year to the next.

The method of calculating exposure is based on the number of PE to the drug.

Therefore, it is difficult to estimate the number of individual patients exposed to icatibant.

Although up to 3-doses of icatibant can be used within a 24-hour period to treat an attack of HAE, experience from clinical trials shows that an average of 1.1 doses is required to treat each attack. Therefore, PE can be calculated as follows:

Estimated PEs = distributed doses /1.1

SV.1.2. Exposure

As of 11-July-2024, the cumulative post-authorisation exposure is approximately 983,778 patient exposures (PEs).

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

No potential for illegal misuse has been identified.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1. IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

None

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Not applicable.

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

None

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

None

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised):

None

Known risks that do not impact the risk-benefit profile:

None

Other reasons for considering the risks not important:

None

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks	Risk-benefit impact
Injection Site Reactions	All injection site reactions with icatibant in HAE subjects were non-serious and in general, resolved without further intervention.

Important Potential Risks	Risk-benefit impact
Deterioration of Cardiac Function under Ischaemic Conditions due to bradykinin antogonism	Potentially fatal in patients with acute cardiac ischaemia or unstable angina.

Important Potential Risks	Risk-benefit impact
Partial Bradykinin Agonism (Excluding Injection Site Reactions)	No risk expected when the labelled dose and regimen is used for treatment of acute HAE attacks.
Antigenicity manifesting as drug hypersensitivity and lack of efficacy	No hypersensitivity or anaphylactic reactions with positive antigenicity were reported with icatibant.
Lack of Efficacy	As HAE attacks with mucosal swellings in the larynx and tongue region cause obstruction in the upper airways, lack of efficacy may lead to life-threatening situations or death by asphyxiation
Medication Errors	Medication errors may result in lack of efficacy; however, medication errors can be prevented by following the instructions for use in the label. For children, a detailed description of the dose volumes to be administered based on weight is provided in the SmPC.
Effect on reproductive hormone levels in pubertal/ post-pubertal children	Changes in reproductive hormone levels may result in effects concentration of luteal phase progesterone and luteal function, or on menstrual cycle length in females, or on sperm count, motility, and morphology in males.

Missing information	Risk-benefit impact
Use in pregnant and lactating women	No clinical data on the use in pregnant and/or lactating women.
Use in children below 2 years of age	No clinical data in children below 2 years of age.

SVII.2. NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Since there are no additional risk minimization measures (aRMMs) or additional PV activities in place to further characterize these safety concerns, the MAH decided to remove these safety concerns in accordance with definition of safety concerns as per GVP module V revision 2. However, the MAH will continue to monitor these in routine PV activities.

Important identified risk: Injection site reactions: Injection site reactions is considered a well-characterized ADR for Firazyr and is already listed in the Firazyr labels (SmPC). Additionally, the Pharmacovigilance Risk Assessment Committee (PRAC) recommended to remove this risk in the summary of safety concerns for Firazyr (EMEA/H/C/PSUSA/00001714/202107).

Important potential risk: Deterioration of Cardiac Function under Ischemic Conditions – Although theoretical risk still exists, the cumulative review of this topic did not reveal new significant information. There is no reasonable expectation that any additional pharmacovigilance activity can further characterise the risk.

Important potential risk: Partial Bradykinin Agonism (Excluding Injection Site Reactions) - No significant new information emerged from the cumulative review. There is no reasonable expectation that any additional pharmacovigilance activity can further characterise the risk.

Important potential risk: Antigenicity manifesting as drug hypersensitivity and lack of efficacy - No significant new information emerged from this cumulative review. There is no reasonable expectation that any additional pharmacovigilance activity can further characterise the risk.

Important potential risk: Lack of efficacy - No significant new information emerged from the cumulative review. There is no reasonable expectation that any additional pharmacovigilance activity can further characterise the risk.

Important potential risk: Medication errors - No risk-specific trend or pattern observed for medication errors and its co-reported adverse events. No significant safety or efficacy related issues were associated with medication errors. There is no reasonable expectation that any additional pharmacovigilance activity can further characterise the risk.

Important potential risk: Effect on reproductive hormone levels in pubertal/-post-pubertal children - No cases with changes of reproductive hormone levels were identified from cumulative review. The data available, including pediatric data, did not show any new safety concerns. Based on Zanichelli et al., (2013), the median age at first HAE symptoms was 12.0 years but the median [range] delay in diagnosis in HAE type I and II patients was 8.5 years, hence, the age of diagnosis for someone with HAE is usually after puberty. There is no reasonable expectation that any additional pharmacovigilance activity can further characterise the risk.

Missing information: Use in children below 2 years of age - No particular patterns or trends of safety concerns could be identified from the cumulative review. The drug is indicated for treatment of acute attack of HAE for patients with C1 esterase inhibitor deficiency aged 2 years and older. There is no reasonable expectation that any additional pharmacovigilance activity can further characterise this missing information.

SVII.3. DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

SVII.3.1. Presentation of important identified risks and important potential risks

None

SVII.3.2. Presentation of the missing information

Use in pregnant and lactating women	
Evidence source	There is no or limited data from the use of icatibant in pregnant and lactating women. **Population in need of further characterisation:** Safety profile among pregnant and lactating patients.

[redacted]

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Use in Pregnant and Lactating Women

[redacted]

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

None

Specific adverse reaction follow-up questionnaires for safety concern:

None

Other forms of routine pharmacovigilance activities for safety concern:

None

III.2. ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

None

III.3. SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Not applicable				

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable

[redacted]

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. ROUTINE RISK MINIMISATION MEASURES

Table V.1. Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Use during pregnancy and lactation	**Routine risk communication:** Section 4.6 in the EU SmPC **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None proposed. **Other routine risk minimisation measures beyond the Product Information:** None proposed.

V.2. ADDITIONAL RISK MINIMISATION MEASURES

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. SUMMARY OF RISK MINIMISATION MEASURES

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use during pregnancy and lactation	**Routine risk minimisation measures:** Section 4.6 of the SmPC **Additional risk minimisation measures:** None proposed	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** No pharmacovigilance activities

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for FIRAZYR (icatibant acetate)

This is a summary of the risk management plan (RMP) for FIRAZYR. The RMP details important risks of FIRAZYR, how these risks can be minimised, and how more information will be obtained about FIRAZYR's risks and uncertainties (missing information).

FIRAZYR 's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how FIRAZYR should be used.

This summary of the RMP for FIRAZYR should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of FIRAZYR 's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

FIRAZYR is authorised for symptomatic treatment of acute attacks of HAE in adults, adolescents, and children aged 2 years and older with C1-INH deficiency. It contains icatibant acetate as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of FIRAZYR's benefits can be found in FIRAZYR's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

FIRAZYR's benefits can be found in FIRAZYR's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/firazyr.

The link to the EPAR summary will be provided to the applicant as part of the cover letter in the CHMP opinion package. MAHs should use the same link for updates related to post-authorisation procedures.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of FIRAZYR, together with measures to minimise such risks and the proposed studies for learning more about FIRAZYR 's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of FIRAZYR is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Firazyr are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Firazyr. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Currently, no important risks are associated with this product for inclusion in this EU RMP.

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	Use in Pregnant and Lactating Women

II.B Summary of important risks

Not applicable.

II.C. Post-authorisation development plan

II.C.1. Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of FIRAZYR.

II.C.2. Other studies in post-authorisation development plan

There are no studies required for FIRAZYR.

PART VII: ANNEXES

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[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Annex 4: Specific adverse drug reaction follow-up forms

Not applicable

[redacted]

[redacted]

[redacted]

Annex 6: Details of proposed additional risk minimisation activities (if applicable)

Not applicable

[redacted]