ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT

Firazyr 30 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection. The solution is a clear and colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Posology

The recommended dose 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.

Special populations

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

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

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

Renal impairment
No dose adjustment is required in patients with renal impairment.
**Paediatric population**
The safety and efficacy of Firazyr in children aged 0-18 years has not been established.

No data are available.

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

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

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

Each Firazyr syringe is intended for single use only.

Firazyr solution for injection should be injected slowly due to the volume to be administered (3 ml).

### 4.3 Contraindications

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

### 4.4 Special warnings and precautions for use

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

**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 Firazyr 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.

**Self-administration**
For patients who never received Firazyr previously, the first treatment should be given in a medical institution or under the guidance of a physician.

In case of insufficient relief or recurrence of symptoms after self-treatment, it is recommended that the patient should seek medical advice and that subsequent doses are given in a medical institution (see section 4.2).

Patients experiencing a laryngeal attack should always seek medical advice and be observed in a medical institution also after having taken the injection at home.
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 Firazyr with angiotensin-converting-enzyme (ACE) inhibitors has not been studied. ACE inhibitors are contraindicated in HAE patients due to possible enhancement of bradykinin levels.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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

Breast-feeding

Icatibant is excreted in the milk of lactating rats at concentrations similar to those in maternal blood. No effects were detected in the post-natal development of rat pups.

It is unknown whether icatibant is excreted in human breast milk but it is recommended that breastfeeding women, who wish to take Firazyr, should not breastfeed for 12 hours after treatment.

Fertility

In both rats and dogs, repeated use of icatibant resulted in effects on reproductive organs. Icatibant had no effect on the fertility of male mice and rats (see section 5.3). In a study of 39 healthy adult men and women treated with 30 mg every 6 hours for 3 doses every 3 days for a total of 9 doses, there were no clinically significant changes from baseline in basal and GnRH-stimulated concentration of reproductive hormones in either females or males. There were no significant effects of icatibant on the concentration of luteal phase progesterone and luteal function, or on menstrual cycle length in females and there were no significant effects of icatibant on sperm count, motility and morphology in males. The dosing regimen used for this study is unlikely to be sustained in the clinical setting.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

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

The frequency of adverse reactions listed in Table 1 is defined using the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 1: Adverse reactions reported with icatibant

<table>
<thead>
<tr>
<th>System Organ Class (incidence category)</th>
<th>Preferred Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>(Common, ≥1/100 to &lt;1/10)</td>
<td>Dizziness</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>(Common, ≥1/100 to &lt;1/10)</td>
<td>Nausea</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
</tr>
<tr>
<td>(Common, ≥1/100 to &lt;1/10)</td>
<td>Rash</td>
</tr>
<tr>
<td></td>
<td>Erythema</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Injection site reactions*</td>
</tr>
<tr>
<td>(Very Common, ≥1/10)</td>
<td></td>
</tr>
<tr>
<td>(Common, ≥1/100 to &lt;1/10)</td>
<td>Pyrexia</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
</tr>
<tr>
<td>(Common, ≥1/100 to &lt;1/10)</td>
<td>Transaminase increased</td>
</tr>
</tbody>
</table>

* Injection site bruising, Injection site hematoma, Injection site burning, Injection site erythema, Injection site hypoesthesia, Injection site irritation, Injection site numbness, Injection site edema, Injection site pain, Injection site pressure sensation, Injection site pruritus, Injection site swelling, Injection site urticaria, and Injection site warmth.

Description of selected adverse reactions

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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.
5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

HAE (an autosomal dominant disease) is caused by an absence or dysfunction of C1-esterase-inhibitor. HAE attacks are accompanied by an increased release of bradykinin, which is the key mediator in the development of the clinical symptoms.

HAE manifests as intermittent attacks of subcutaneous and/or sub mucosal oedema involving the upper respiratory tract, the skin and the gastrointestinal tract. An attack usually lasts between 2 to 5 days.

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

Pharmacodynamic effects

In healthy young subjects, icatibant administered in doses of 0.8 mg/kg over 4 hours; 1.5 mg/kg/day or 0.15 mg/kg/day for 3 days, development of bradykinin-induced hypotension, vasodilatation and reflex tachycardia was prevented. Icatibant was shown to be a competitive antagonist when the bradykinin challenge dose was increased 4-fold.

Clinical efficacy and safety

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

Phase III clinical studies (FAST-1 and FAST-2) were randomized, double-blind, controlled trials and had identical designs except for the comparator (one with oral tranexamic acid as the comparator and one placebo controlled). 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. The primary efficacy endpoint was the time to onset of symptom relief using a visual analogue scale (VAS). Table 2 shows the efficacy results for these studies.

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

In these studies, patients on icatibant had a faster median time to onset of symptom relief (2.0, 2.5 and 2.0 hours, respectively) compared to tranexamic acid (12.0 hours) and placebo (4.6 and 19.8 hours). The treatment effect of icatibant was confirmed by secondary efficacy endpoints.
In an integrated analysis of these controlled Phase III studies, the time to onset of symptom relief and time to onset of primary symptom relief were similar regardless of age group, sex, race, weight or whether or not the patient used androgens or antifibrinolytic agents.

Response was also consistent across repeated attacks in the controlled Phase III trials. A total of 237 patients were treated with 1,386 doses of 30 mg icatibant for 1,278 attacks of acute HAE. In the first 15 Firazyr treated attacks (1,114 doses for 1,030 attacks), the median times to onset of symptom relief were similar across attacks (2.0 to 2.5 hours). 92.4% of these attacks of HAE were treated with a single dose of Firazyr.

### Table 2. Efficacy results for FAST-1 and FAST-2

<table>
<thead>
<tr>
<th>Controlled Clinical Study of FIRAZYR vs Tranexamic acid or Placebo: Efficacy Results</th>
<th>FAST-2</th>
<th>FAST-1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Icatibant</td>
<td>Tranexamic acid</td>
</tr>
<tr>
<td><strong>Number of subjects in ITT Population</strong></td>
<td>36</td>
<td>38</td>
</tr>
<tr>
<td>Baseline VAS(mm)</td>
<td>63.7</td>
<td>61.5</td>
</tr>
<tr>
<td>Change from baseline to 4 hours</td>
<td>-41.6</td>
<td>-14.6</td>
</tr>
<tr>
<td>Difference between treatments (95% CI, p-value)</td>
<td>-27.8 (-39.4, -16.2) p &lt; 0.001</td>
<td>Difference between treatments (95% CI, p-value)</td>
</tr>
<tr>
<td>Change from baseline to 12 hours</td>
<td>-54.0</td>
<td>-30.3</td>
</tr>
<tr>
<td>Difference between treatments (95% CI, p-value)</td>
<td>-24.1 (-33.6, -14.6) p &lt; 0.001</td>
<td>Difference between treatments (95% CI, p-value)</td>
</tr>
<tr>
<td>Median time to onset of symptom relief (hours)</td>
<td>Median time to onset of symptom relief (hours)</td>
<td></td>
</tr>
<tr>
<td>All episodes (N = 74)</td>
<td>2.0</td>
<td>12.0</td>
</tr>
<tr>
<td>Response rate (% CI) at 4 hours after start of treatment</td>
<td>Response rate (% CI) at 4 hours after start of treatment</td>
<td></td>
</tr>
<tr>
<td>All episodes (N = 74)</td>
<td>80.0 (63.1, 91.6)</td>
<td>30.6 (16.3, 48.1)</td>
</tr>
<tr>
<td>Median time to onset of symptom relief: all symptoms (hours): Abdominal pain</td>
<td>Median time to onset of symptom relief: all symptoms (hours): Abdominal pain</td>
<td></td>
</tr>
<tr>
<td>Skin swelling</td>
<td>1.6</td>
<td>3.5</td>
</tr>
<tr>
<td>Skin pain</td>
<td>2.6</td>
<td>18.1</td>
</tr>
<tr>
<td>Median time to almost complete symptom relief (hours)</td>
<td>Median time to almost complete symptom relief (hours)</td>
<td></td>
</tr>
<tr>
<td>Median time to almost complete symptom relief (hours)</td>
<td>1.5</td>
<td>12.0</td>
</tr>
</tbody>
</table>
Controlled Clinical Study of FIRAZYR vs Tranexamic acid or Placebo: Efficacy Results

<table>
<thead>
<tr>
<th>FAST-2</th>
<th>Icatibant</th>
<th>Tranexamic acid</th>
<th>FAST-1</th>
<th>Icatibant</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All episodes (N = 74)</td>
<td>10.0</td>
<td>51.0</td>
<td>All episodes (N = 56)</td>
<td>8.5</td>
<td>19.4</td>
</tr>
<tr>
<td>Median time to regression of symptoms, by patient (hours)</td>
<td>0.8</td>
<td>7.9</td>
<td>Median time to regression of symptoms, by patient (hours)</td>
<td>0.8</td>
<td>16.9</td>
</tr>
<tr>
<td>All episodes (N = 74)</td>
<td>1.5</td>
<td>6.9</td>
<td>All episodes (N = 56)</td>
<td>1.0</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Table 3. Efficacy results for FAST-3

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Statistic</th>
<th>Firazyr</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to Onset of Symptom Relief -- Composite VAS (hrs)</td>
<td>Median</td>
<td>2.0</td>
<td>19.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(n = 43)</td>
<td>(n=45)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Statistic</th>
<th>Firazyr</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to Onset of Primary Symptom Relief (hrs)</td>
<td>Median</td>
<td>1.5</td>
<td>18.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Change in Composite VAS Score at 2 hrs after treatment</td>
<td>Mean</td>
<td>-19.74</td>
<td>-7.49</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Change in Composite Subject-Assessed Symptom Score at 2 hours</td>
<td>Mean</td>
<td>-0.53</td>
<td>-0.22</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Change in Composite Investigator-Assessed Symptom Score at 2 hours</td>
<td>Mean</td>
<td>-0.44</td>
<td>-0.19</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Time to Almost Complete Symptom Relief (hrs)</td>
<td>Median</td>
<td>8.0</td>
<td>36.0</td>
<td>0.012</td>
</tr>
<tr>
<td>Time to Subject-Assessed Initial Symptom Improvement (hrs)</td>
<td>Median</td>
<td>0.8</td>
<td>3.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Time to Investigator-Assessed Initial Visual Symptom Improvement (hrs)</td>
<td>Median</td>
<td>0.8</td>
<td>3.4</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
A total of 66 patients with attacks of HAE affecting the larynx were treated in these controlled Phase III clinical trials. The results were similar to patients with non-laryngeal attacks of HAE with respect to time to onset of symptom relief.

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 30 minutes.

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

Elimination
Icatibant is mainly eliminated by metabolism with less than 10% of the dose eliminated in the urine as unchanged drug. Clearance is about 15-20 l/h and independent of dose. The terminal plasma half-life is about 1-2 hours.

Biotransformation
Icatibant is extensively metabolized by proteolytic enzymes to inactive metabolites that are primarily excreted in the urine.

In vitro studies have confirmed that icatibant is not degraded by oxidative metabolic pathways and is not an inhibitor of major cytochrome P450 (CYP) isoenzymes (CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4) and is not an inducer of CYP 1A2 and 3A4.

Special populations
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. Data suggests that gender and weight do not have a significant influence on icatibant pharmacokinetics.

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

5.3 Preclinical safety data

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

Maximum daily exposures defined by area under the curve (AUC) at the No Observed Adverse Effect Levels (NOAEL) in the 9-month study in dog were 2.3 times the AUC in humans after a subcutaneous dose of 30 mg. A NOAEL was not measurable in the rat study, however, all of the findings from that study showed either completely or partially reversible effects in treated rats. Adrenal gland hypertrophy was observed at all doses tested in rats. Adrenal gland hypertrophy was seen to reverse after cessation of icatibant treatment. The clinical relevance of the adrenal gland findings is unknown.

Icatibant had no effect on the fertility of male mice (top dose 80.8 mg/kg/day) and rats (top dose 10 mg/kg/day).
In a 2 year study to evaluate the carcinogenic potential of icatibant in rats, daily doses giving exposure levels up to approximately 2-fold that achieved after a therapeutic dose in humans had no effect on the incidence or morphology of tumours. Results do not indicate a carcinogenic potential for icatibant.

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

Icatibant was not teratogenic when administered by 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 a juvenile toxicity study in which sexually immature rats were treated daily with 3 mg/kg for 7 weeks, atrophy of testes and epididymides were observed. Similar effects of icatibant on reproductive tissue were seen in sexually mature rats and dogs. These tissue findings were consistent with reported effects on gonadotrophins and during the subsequent treatment-free period appear to be reversible.

Icatibant did not elicit any cardiac conduction change *in vitro* (hERG channel) or *in vivo* in normal dogs or in various dog models (ventricular pacing, physical exertion and coronary ligation) where no associated hemodynamic changes were observed. Icatibant has been shown to aggravate induced cardiac ischemia in several non-clinical models, although a detrimental effect has not consistently been shown in acute ischemia.

### 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

2 years.

#### 6.4 Special precautions for storage

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

#### 6.5 Nature and contents of container

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

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

Not all pack sizes may be marketed.
6.6 Special precautions for disposal

The solution should be clear and colourless and free from visible particles. For single use only.

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

7. MARKETING AUTHORISATION HOLDER

Shire Orphan Therapies GmbH
Friedrichstrasse 149
D-10117 Berlin
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/461/001
EU/1/08/461/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 July 2008
Date of latest renewal: 13 March 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency
ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT
A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Shire Pharmaceuticals Ireland Limited
5 Riverwalk
Citywest Business Campus
Dublin 24
Ireland.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as a result of an updated (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
1. **NAME OF THE MEDICINAL PRODUCT**

Firazyr 30 mg solution for injection in pre-filled syringe
Icatibant

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

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

3. **LIST OF EXCIPIENTS**

Contains: acetic acid glacial, sodium hydroxide, sodium chloride, water for injections.

4. **PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection
One pre-filled syringe
One 25G needle

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Subcutaneous use
Read the package leaflet before use
For single use only

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP

9. **SPECIAL STORAGE CONDITIONS**

Do not store above 25ºC. Do not freeze.
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPLICABLE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

   Marketing Authorisation Holder
   Shire Orphan Therapies GmbH
   Friedrichstrasse 149
   D-10117 Berlin
   Germany

12. **MARKETING AUTHORISATION NUMBER(S)**

   EU/1/08/461/001

13. **BATCH NUMBER**

   Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

   Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

   Firazyrr 30 mg
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Outer Carton of Multi-Pack (Including Blue Box)

1. NAME OF THE MEDICINAL PRODUCT

Firazyr 30 mg solution for injection in pre-filled syringe
Icatibant

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains: acetic acid glacial, sodium hydroxide, sodium chloride, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
Multipack containing three pre-filled syringes and three 25G needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use
For single use only

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25ºC. Do not freeze.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder
Shire Orphan Therapies GmbH
Friedrichstrasse 149
D-10117 Berlin
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/461/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Firazyrr 30 mg
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Intermediate Carton of Multi-Pack (Without Blue Box)

#### 1. NAME OF THE MEDICINAL PRODUCT

Firazyr 30 mg solution for injection in pre-filled syringe  
Icatibant

#### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

#### 3. LIST OF EXCIPIENTS

Contains: acetic acid glacial, sodium hydroxide, sodium chloride, water for injections.

#### 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection  
One pre-filled syringe and one 25G needle.  
Component of a multipack, can’t be sold separately.

#### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use  
Read the package leaflet before use  
For single use only

#### 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

#### 7. OTHER SPECIAL WARNING(S), IF NECESSARY

#### 8. EXPIRY DATE

EXP

#### 9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Do not freeze.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder
Shire Orphan Therapies GmbH
Friedrichstrasse 149
D-10117 Berlin
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/461/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Firazyr 30 mg
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

{Blister tray lid}

<table>
<thead>
<tr>
<th>1. <strong>NAME OF THE MEDICINAL PRODUCT</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Firazyr 30 mg solution for injection in pre-filled syringe</td>
</tr>
<tr>
<td>Icatibant</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. <strong>NAME OF THE MARKETING AUTHORISATION HOLDER</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Shire Orphan Therapies GmbH</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. <strong>EXPIRY DATE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. <strong>BATCH NUMBER</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. <strong>OTHER</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous use</td>
</tr>
</tbody>
</table>
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Syringe label

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Firazyr 30 mg
Icatibant
sc

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

30 mg/3 ml

6. OTHER

Shire Orphan Therapies GmbH
B. PACKAGE LEAFLET
Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:
1. What Firazyr is and what it is used for
2. What you need to know before you use Firazyr
3. How to use Firazyr
4. Possible side effects
5. How to store Firazyr
6. Contents of the pack and other information

1. What Firazyr is and what it is used for

Firazyr contains the active substance icatibant.

Firazyr is used for treating the symptoms of hereditary angioedema (HAE) in adult patients. In HAE levels of a substance in your bloodstream called bradykinin are increased and this leads to symptoms like swelling, pain, nausea, and diarrhoea. Firazyr blocks the activity of bradykinin and therefore ends the further progression of the symptoms.

2. What you need to know before you use Firazyr

Do not use Firazyr
- If you are allergic to icatibant, or any of the other ingredients of this medicine (listed in section 6).

Warning and precautions
Talk to your doctor before taking Firazyr:

Some of the side effects connected with Firazyr are similar to the symptoms of your disease. Tell your doctor immediately if you notice that your symptoms of the attack get worse after you received Firazyr
- if you are suffering from angina (reduced blood flow to the heart muscle)
- if you have recently suffered a stroke

In addition:
- You must be trained on subcutaneous (under the skin) injection technique before you self-inject Firazyr.
- Immediately after you self-inject Firazyr or your caregiver injects you with Firazyr while you are experiencing a laryngeal attack (obstruction of the upper airway), you must seek medical care in a medical institution.

- If your symptoms are not resolved following one self-administered injection of Firazyr, you should seek medical advice regarding additional injections of Firazyr. Up to 2 additional injections may be given within 24 hours.

Children and adolescents
Firazyr is not recommended for use in children and adolescents under 18 years of age because it has not yet been studied in this age group.

Other medicines and Firazyr
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Firazyr is not known to interact with other medicines. If you are taking a medicine known as an Angiotensin Converting Enzyme (ACE) inhibitor (for example: captopril, enalapril, ramipril, quinapril, lisinopril) which is used to lower your blood pressure or for any other reason, you should inform your doctor before receiving Firazyr.

Pregnancy and breast feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor before starting to use Firazyr.

If you are breast-feeding you should not breast-feed for 12 hours after you have last received Firazyr.

Driving and using machines
Do not drive or use machines if you feel tired or dizzy as a result of your HAE attack or after using Firazyr.

Firazyr contains a small amount of sodium
The injection solution contains less than 1 mmol (23 milligrams) of sodium, so it is essentially ‘sodium-free’.

3. How to use Firazyr

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

If you have never received Firazyr previously, your first dose of Firazyr will always be injected by your doctor or nurse. Your doctor will tell you when it is safe for you to go home. After discussion with your doctor or nurse and after training in subcutaneous (under the skin) injection technique, you may be able to inject yourself with Firazyr or your caregiver may inject Firazyr for you when you have an HAE attack. It is important that Firazyr is injected subcutaneously (under the skin) as soon as you notice the attack of hereditary angioedema. Your healthcare provider will teach you and your caregiver how to safely inject Firazyr by following the instructions in the Package Leaflet.

When and how often should you use Firazyr?
- Your doctor has determined the exact dose of Firazyr and will tell you how often it should be used. The recommended dose of Firazyr is one injection (3 ml, 30 mg) applied subcutaneously (under the skin) as soon as you notice the attack of hereditary angioedema (for example increased skin swelling, particularly affecting the face and neck, or increasing tummy pain).

If you experience no relief of symptoms after 6 hours, you should seek medical advice regarding additional injections of Firazyr. Up to 2 additional injections may be given within 24 hours.
You should not have more than 3 injections in a 24 hour period and if you require more than 8 injections in a month, you should seek medical advice.

How should Firazyr be administered?
Firazyr is intended for subcutaneous injection (under the skin). Each syringe should only be used once.

Firazyr is injected with a short needle into the fatty tissue under the skin in the abdomen (tummy).

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

The following step-by-step instruction is intended for self-administration only.

The instructions include the following main steps:

1) General Important Information
2) Preparing the syringe and needle for injection
3) Preparing the injection site
4) Injecting the solution
5) Disposal of the injection material

Step-by-Step Instructions for Injection

1) General Important Information

- Wash your hands with soap and water before beginning the process.
- Open the blister by peeling back the seal.
- Remove the pre-filled syringe from the blister tray.
- Remove the cap from the end of the pre-filled syringe by unscrewing the cap.
- Put down the pre-filled syringe after unscrewing the cap.
2) Preparing the syringe and needle for injection

• Remove the needle cap from the blister.
• Remove the seal from the needle cap (the needle should be still in the needle cap).

• Grip the syringe firmly. Carefully attach the needle to the pre-filled syringe containing the colourless solution.
• Screw the pre-filled syringe on the needle still fixed in the needle cap.
• Remove the needle from the needle cap by pulling the syringe. Do not pull up on the plunger.
• The syringe is now ready for injection.
3) Preparing the injection site

- Choose the injection site. The injection site should be a skin fold on your abdomen approximately 5-10 cm (2-4 inches) below your navel on either side. This area should be at least 5 cm (2 inches) away from any scars. Do not choose an area that is bruised, swollen, or painful.
- Clean the injection site with a rubbing alcohol pad and allow it to dry.

4) Injecting the Solution

- Hold the syringe in one hand between two fingers with your thumb at the bottom of the plunger.
- Make sure that there is no air bubble in the syringe by pressing the plunger until the first drop appears on the tip of the needle.
4) Injecting the Solution (continued)

- Hold syringe between 45-90 degrees angle to skin with needle facing the skin.
- Keeping the syringe in one hand, use your other hand to gently hold a fold of skin between your thumb and fingers at the previously disinfected injection site.
- Hold the fold of skin, bring the syringe to the skin and quickly insert the needle into the skin fold.
- Slowly push the plunger of the syringe with a steady hand until all the fluid is injected into the skin and no liquid remains in the syringe.
- Press slowly so that this takes approximately 30 seconds.
- Release the skin fold and gently pull the needle out.

5) Disposal of the injection material

- Discard the syringe, needle and needle cap into the sharp container for throwing away waste that might hurt others if not handled properly.
4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Almost all patients receiving Firazyr will experience a reaction at the site of the injection (such as skin irritation, swelling, pain, itchiness, redness of the skin and burning sensation). These effects are usually mild and clear up without the need for any additional treatment.

The very common side effects (may affect more than 1 in 10 people) are:
Additional injection site reactions (pressure sensation, bruising, reduced sensation and/or numbness, raised itchy skin rash and warmth).

The common side effects (may affect up to 1 in 10 people) are:
- Feeling sick
- Headache
- Dizziness
- Fever
- Itching
- Rash
- Skin redness
- Abnormal liver function test

Tell your doctor immediately if you notice that the symptoms of your attack get worse after you received Firazyr.

If you get any side effects talk to your doctor. This includes any possible side effects not listed in this leaflet.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Firazyr

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the label after ‘EXP’. The expiry date refers to the last day of that month.

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

Do not use this medicine if you notice that the syringe or needle packaging is damaged or if there are any visible signs of deterioration, for example if the solution is cloudy, if it has floating particles, or if the colour of the solution has changed.

Do not throw away any medicines via waste water or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Firazyr contains
The active substance is icatibant. Each pre-filled syringe contains 30 milligrams of icatibant (as acetate). The other ingredients are sodium chloride, acetic acid glacial, sodium hydroxide and water for injection.
**What Firazyr looks like and contents of the pack**
Firazyr is presented as a clear, colourless solution for injection in a pre-filled glass syringe of 3 ml. Hypodermic needle is included in the pack.

Firazyr is available as a single pack containing one pre-filled syringe with one needle or as a multipack containing three pre-filled syringes with three needles.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**
Shire Orphan Therapies GmbH  
Friedrichstrasse 149  
D-10117 Berlin  
Germany

**Manufacturer**
Shire Pharmaceuticals Ireland Limited  
5 Riverwalk  
Citywest Business Campus  
Dublin 24  
Ireland

**This leaflet was last revised in**

**Other sources of information**
Detailed information on this medicine is available on the European Medicines Agency website:  
[http://www.ema.europa.eu](http://www.ema.europa.eu). There are also links to other websites about rare diseases and treatments.