ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Icatibant Accord 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, practically free from foreign particles.
pH: 5.0 to 6.0
Osmolality: 280 to 340 mOsmol/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Icatibant Accord is indicated for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults, adolescents and children aged 2 years and older, with C1-esterase-inhibitor deficiency.

4.2 Posology and method of administration

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

Posology

Adults

The recommended dose for adults is a single subcutaneous injection of Icatibant Accord 30 mg.

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

In the clinical trials, not more than 8 injections of Icatibant Accord per month have been administered.

Paediatric population

The recommended dose of Icatibant Accord based on body weight in children and adolescents (aged 2 to 17 years) is provided in table 1 below.

Table 1: Dose regimen for paediatric patients

Body Weight	Dose (Injection Volume)
12 kg to 25 kg	10 mg (1.0 ml)
26 kg to 40 kg	15 mg (1.5 ml)
41 kg to 50 kg	20 mg (2.0 ml)
51 kg to 65 kg	25 mg (2.5 ml)
>65 kg	30 mg (3.0 ml)

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

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

Elderly

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

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

Hepatic impairment

No dose adjustment is required in patients with hepatic impairment.

Renal impairment

No dose adjustment is required in patients with renal impairment.

Method of administration

Icatibant Accord is intended for subcutaneous administration preferably in the abdominal area.

Icatibant Accord solution for injection should be injected slowly due to the volume to be

administered. Each Icatibant Accord syringe is intended for single use only.

Refer to the patient information leaflet for instructions for use.

Caregiver/self-administration

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

Adults

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

Children and adolescents aged 2-17 years

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Laryngeal attacks

Patients with laryngeal attacks should be managed in an appropriate medical institution after injection until the 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 Icatibant Accord 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.

Caregiver/self-administration

For patients who have never received Icatibant Accord 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 or administration by a caregiver, it is recommended that the patient or caregiver should seek medical advice. For adults, subsequent doses that may be required for the same attack should be administered within a medical institution (see section 4.2). There are no data on administering subsequent doses for the same attack in adolescents or children.

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

Sodium content

This medicinal product contains less than 1 mmol (23 milligrams) of sodium per syringe, that is to say essentially 'sodium-free.'

Paediatric population

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

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

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Icatibant Accord 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 Icatibant Accord, 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

Icatibant Accord has minor influence on the ability to drive and use machines. Fatigue, lethargy, tiredness, somnolence, and dizziness have been reported following the use of Icatibant Accord. 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 Icatibant administered subcutaneously by a healthcare professional. Icatibant 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).
All adverse reactions from post-marketing experience are *italicised.*

Table 2: Adverse reactions reported with icatibant

System organ class (incidence category)	**Preferred term**
Nervous system disorders (Common, ≥1/100 to <1/10)	 Dizziness Headache
Gastrointestinal disorders (Common, ≥1/100 to <1/10)	 Nausea
Skin and subcutaneous tissue disorders (Common, ≥1/100 to <1/10) *(Unknown)*	 Rash Erythema Pruritus *Urticaria*
General disorders and administration site conditions (Very Common, ≥1/10) (Common, ≥1/100 to <1/10)	 Injection site reactions * Pyrexia
Investigations (Common, ≥1/100 to <1/10)	 Transaminases increased
* Injection site bruising, Injection site hematoma, Injection site burning, Injection site erythema, Injection site hypoesthesia, Injection site irritation, Injection site numbness, Injection site edema, Injection site pain, Injection site pressure sensation, Injection site pruritus, Injection site swelling, Injection site urticaria, and Injection site warmth.	

Paediatric population

A total of 32 paediatric patients (8 children aged 2 to 11 years and 24 adolescents aged 12 to 17 years) with HAE were exposed to treatment with icatibant during clinical studies. Thirty-one patients received a single dose of icatibant and 1 patient (an adolescent) received icatibant for two HAE attacks (in total, two doses). Icatibant was administered by subcutaneous injection at a dose of 0.4 mg/kg based on body weight to a maximum dose of 30 mg.

The majority of paediatric patients who were treated with subcutaneous icatibant experienced injection site reactions such as erythema, swelling, burning sensation, skin pain and itching/pruritus; these were found to be mild to moderate in severity and consistent with reactions that have been reported in adults. Two paediatric patients experienced injection site reactions which were assessed as severe and which were completely resolved within 6 hours. These reactions were erythema, swelling, burning and warm sensation.

No clinically significant changes in reproductive hormones were observed during clinical studies.

Description of selected adverse reactions

Immunogenicity

Across repeated treatment in adults in the controlled phase III trials, transient positivity to anti-icatibant antibodies was observed in rare cases. All patients maintained efficacy. One Icatibant - treated patient tested positive for anti-icatibant antibodies before and after treatment with Icatibant. 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 .

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

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

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

Pharmacodynamic effects

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

Clinical efficacy and safety

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

Phase III clinical studies (FAST-1 and FAST-2) were randomised, 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 randomised 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 3 shows the efficacy results for these studies.

FAST-3 was a randomised, placebo-controlled, parallel-group study of 98 adult patients with a median age of 36 years. Patients were randomised to receive either icatibant 30 mg or placebo by subcutaneous injection. A subset of patients in this study experienced acute HAE attacks while receiving androgens, antifibrinolytic agents or 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 4 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 Icatibant treated attacks (1,114 doses for 1,030 attacks), the median times to onset of symptom relief were similar across attacks (2.0 to 2.5 hours). 92.4% of these attacks of HAE were treated with a single dose of Icatibant.

Table 3. Efficacy results for FAST-1 and FAST-2

Controlled clinical study of icatibant vs tranexamic acid or placebo: efficacy results					
FAST-2			FAST-1		
	icatibant	Tranexamic acid		icatibant	Placebo
Number of subjects in ITT population	36	38	Number of subjects in ITT population	27	29
Baseline VAS(mm)	63.7	61.5	Baseline VAS(mm)	69.3	67.7
Change from baseline to 4 hours	-41.6	-14.6	Change from baseline to 4 hours	-44.8	-23.5
Difference between treatments (95% CI, p-value)	-27.8 (-39.4, -16.2) p < 0.001		Difference between treatments (95% CI, p-value)	-23.3 (-37.1, -9.4) p = 0.002	
Change from baseline to 12 hours	-54.0	-30.3	Change from baseline to 12 hours	-54.2	-42.4
Difference between treatments (95% CI, p-value)	-24.1 (-33.6, -14.6) p < 0.001		Difference between treatments (95% CI, p-value)	-15.2 (-28.6, -1.7) p = 0.028	
Median time to onset of symptom relief (hours)			Median time to onset of symptom relief (hours)		
All episodes (N = 74)	2.0	12.0	All episodes (N = 56)	2.5	4.6
Response rate (%, CI) at 4 hours after start of treatment			Response rate (%, CI) at 4 hours after start of treatment		
All episodes (N = 74)	80.0 (63.1, 91.6)	30.6 (16.3, 48.1)	All episodes (N = 56)	66.7 (46.0,83.5)	46.4 (27.5, 66.1)
Median time to onset of symptom relief: all symptoms (hours): Abdominal pain Skin swelling Skin pain	 1.6 2.6 1.5	 3.5 18.1 12.0	Median time to onset of symptom relief: all symptoms (hours): Abdominal pain Skin swelling Skin pain	 2.0 3.1 1.6	 3.3 10.2 9.0
Median time to almost complete symptom relief (hours)			Median time to almost complete symptom relief (hours)		
All episodes (N = 74)	10.0	51.0	All episodes (N = 56)	8.5	19.4
Median time to regression of symptoms, by patient (hours)			Median time to regression of symptoms, by patient (hours)		
All episodes (N = 74)	0.8	7.9	All episodes (N = 56)	0.8	16.9
Median time to			Median time to		

Controlled clinical study of icatibant vs tranexamic acid or placebo: efficacy results					
FAST-2			FAST-1		
	icatibant	Tranexamic acid		icatibant	Placebo
overall patient improvement, by physician (hours)			overall patient improvement, by physician (hours)		
All episodes (N = 74)	1.5	6.9	All episodes (N = 56)	1.0	5.7

Table 4. Efficacy results for FAST-3

Efficacy results: FAST-3; controlled Phase -- ITT population				
Endpoint	**Statistic**	**Icatibant**	**Placebo**	**p-value**
		(n = 43)	(n=45)	
Primary endpoint				
Time to onset of symptom relief--composite VAS (hrs)	Median	2.0	19.8	<0.001
Other endpoints				
Time to onset of primary symptom relief (hrs)	Median	1.5	18.5	<0.001
Change in composite VAS score at 2 hrs after treatment	Mean	-19.74	-7.49	<0.001
Change in composite subject-assessed symptom score at 2 hours	Mean	-0.53	-0.22	<0.001
Change in composite investigator-assessed symptom score at 2 hours	Mean	-0.44	-0.19	<0.001
Time to almost complete symptom relief (hrs)	Median	8.0	36.0	0.012
Time to subject-assessed initial symptom improvement (hrs)	Median	0.8	3.5	<0.001
Time to investigator-assessed initial visual symptom improvement (hrs)	Median	0.8	3.4	<0.001

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.

Paediatric population

An open label, non-randomised single-arm study (HGT-FIR-086) was performed with a total of 32 patients. All patients received at least one dose of icatibant (0.4mg/kg body weight up to a maximum dose of 30 mg) and the majority of patients were followed up for a minimum of 6 months. Eleven patients were of prepubertal status and 21 patients were either pubertal or postpubertal.

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

The primary efficacy endpoint was the time to onset of symptom relief (TOSR) measured using a composite investigator-reported symptom score. Time to symptom relief was defined as the duration of time (in hours) taken for improvement of symptoms to occur by a magnitude of 20%.

Overall the median time to onset of symptom relief was 1.0 hour (95% confidence interval, 1.0-1.1 hours). At 1 and 2 hours post treatment, approximately 50% and 90% of patients experienced onset of symptom relief, respectively.

Overall, the median time to minimal symptoms (earliest time post treatment when all symptoms were either mild or absent) was 1.1 hours (95% confidence interval, 1.0-2.0 hours).

5.2 Pharmacokinetic properties

The pharmacokinetics of icatibant has been characterised 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%.

Biotransformation

Icatibant is extensively metabolised 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.

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.

Special populations

Elderly

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

Gender

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

Hepatic and Renal Impairment

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

Race

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

Paediatric population

The pharmacokinetics of icatibant were characterised in paediatric HAE patients in study HGT-FIR-086 (see section 5.1). Following a single subcutaneous administration (0.4 mg/kg up to a maximum of 30 mg), the time to maximum concentration is approximately 30 minutes and the terminal half-life is about 2 hours. There are no observed differences in the exposure to icatibant between HAE patients with and without an attack. Population pharmacokinetic modelling using both adult and paediatric data showed that clearance of icatibant is related to body weight with lower clearance values noted for lower body weights in the paediatric HAE population. Based on modelling for weight banded dosing, the predicted exposure to icatibant in the paediatric HAE population (see section 4.2) is lower than the observed exposure in studies conducted with adult HAE patients.

5.3 Preclinical safety data

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

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

Icatibant had no effect on the fertility of male mice (top dose 80.8 mg/kg/day) and rats (top dose 10 mg/kg/day).

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 SC 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).

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

Icatibant did not elicit any cardiac conduction change *in vitro* (hERG channel) or *in vivo* in normal dogs or in various dog models (ventricular pacing, physical exertion and coronary ligation) where no associated hemodynamic changes were observed. Icatibant has been shown to aggravate induced cardiac 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
Glacial acetic acid (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

This medicinal product does not require any special temperature storage conditions. 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 three pre-filled syringes with three needles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Use in the paediatric population

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

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

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

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

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

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

7. MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center,
Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona, Spain

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1567/001
EU/1/21/1567/002

9. DATE OF FIRST AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS 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 MANUFACTURERS) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Accord Healthcare Polska Sp.z.o.o.
ul. Lutomierska 50,
95-200, Pabianice,
Poland

Accord Healthcare B.V.
Winthontlaan 200, 3526KV Utrecht
The Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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 (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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 marketing authorisation holder (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 the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Icatibant Accord 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: sodium chloride, glacial acetic acid, sodium hydroxide and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe
3 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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 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

Accord Healthcare S.L.U.
World Trade Center,
Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona, Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1567/001
EU/1/21/1567/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Icatibant Accord 30 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL

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

Icatibant Accord 30 mg injection
icatibant
sc use

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

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Icatibant Accord 30 mg solution for injection pre-filled syringe
icatibant

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 Icatibant Accord is and what it is used for

Icatibant Accord contains the active substance icatibant.

Icatibant Accord is used for treating the symptoms of hereditary angioedema (HAE) in adults, adolescents and children aged 2 years and older.

In HAE levels of a substance in your bloodstream called bradykinin are increased and this leads to symptoms like swelling, pain, nausea, and diarrhoea.

Icatibant Accord blocks the activity of bradykinin and therefore ends the further progression of the symptoms.

2. What you need to know before you use Icatibant Accord

Do not use Icatibant Accord If you are allergic to icatibant, or any of the other

ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor before taking Icatibant Accord:
- if you are suffering from angina (reduced blood flow to the heart muscle)
- if you have recently suffered a stroke

Some of the side effects connected with Icatibant Accord 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 Icatibant Accord

In addition:

- You or your caregiver must be trained on subcutaneous (under the skin) injection technique before you self-inject or your caregiver injects you with Icatibant Accord.

- Immediately after you self-inject Icatibant Accord or your caregiver injects you with Icatibant Accord 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- or caregiver administered injection of Icatibant Accord , you should seek medical advice regarding additional injections of Icatibant Accord . For adult patients, up to 2 additional injections may be given within 24 hours.

Children and adolescents

Icatibant Accord is not recommended for use in children under 2 years of age or weighing less than 12 kg because it has not been studied in these patients.

Other medicines and Icatibant Accord

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

Icatibant Accord 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 Icatibant Accord.

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 Icatibant Accord .

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

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 Icatibant Accord .

Icatibant Accord contains sodium

This medicine contains less than 1 mmol sodium (23 milligrams) that is to say essentially 'sodium-free'.

3. How to use Icatibant Accord

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 Icatibant Accord previously, your first dose of Icatibant Accord 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 Icatibant Accord or your caregiver may inject Icatibant Accord for you when you have an HAE attack. It is important that Icatibant Accord is injected subcutaneously (under the skin) as soon as you notice an attack of angioedema. Your healthcare provider will teach you and your caregiver how to safely inject Icatibant Accord by

following the instructions in the Package Leaflet.

When and how often should you use Icatibant Accord?

Your doctor has determined the exact dose of Icatibant Accord and will tell you how often it should be used.

Adults

- The recommended dose of Icatibant Accord is one injection (3 ml, 30 mg) injected subcutaneously (under the skin) as soon as you notice the attack of 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 Icatibant Accord . For adults, 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.**

Children and adolescents aged 2 to 17 years

- The recommended dose of Icatibant Accord is one injection of 1 ml up to a maximum of 3 ml based on body weight injected subcutaneously (under the skin) as soon as you develop symptoms of an angioedema attack (for example increased skin swelling, particularly affecting the face and neck, increasing tummy pain).

- See section on instructions for use for the dose to inject.

- If you are not sure which dose to inject, ask your doctor, pharmacist or nurse.

- **If your symptoms get worse or do not improve, you must seek immediate medical help.**

How should Icatibant Accord be administered?

Icatibant Accord is intended for subcutaneous injection (under the skin). Each syringe should only be used once.

Icatibant Accord 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 instructions are intended for:
- **self-administration (adults)**
- **administration by a caregiver or healthcare professional to adults, adolescents or children aged over 2 years (weighing at least 12 kg).**

The instructions include the following main steps:

1) General Information
2a) Preparing the syringe for children and adolescents (2-17 years) weighing 65 kg or less
2b) Preparing the syringe and needle for injection (all patients)
3) Preparing the injection site
4) Injecting the solution
5) Disposal of the injection material

Step-by-Step Instructions for Injection

1) General Information

- Clean the work area (surface) to be used before beginning the process.
- Wash your hands with soap and water.
- Open the tray by peeling back the seal.
- Remove the pre-filled syringe from the tray.
- Remove the screw cap from the end of the pre-filled syringe by unscrewing the screw cap.
- Put down the pre-filled syringe after unscrewing the screw cap.

2a) Preparing the syringe for children and adolescents (2-17 years) weighing 65 kg or less:

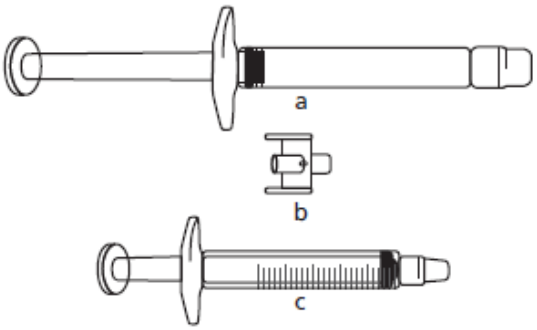
Important information for healthcare professionals and caregivers:

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

a) Icatibant Accord pre-filled syringe (containing icatibant solution)

b) Connector (adapter)

c) 3 ml graduated syringe



The required injection volume in ml should be drawn up in an empty 3 ml graduated syringe (see table below).

Table 1: Dosage regimen for children and adolescents

Body Weight	Injection Volume
12 kg to 25 kg	1.0 ml
26 kg to 40 kg	1.5 ml
41 kg to 50 kg	2.0 ml
51 kg to 65 kg	2.5 ml

Patients weighing **more than 65 kg** will use the full contents of the pre-filled syringe (3 ml).

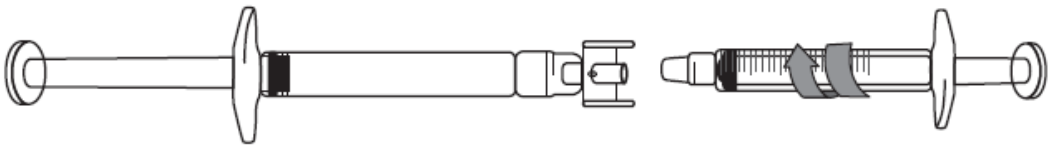
If you are not sure which volume of solution to extract, ask your doctor, pharmacist or nurse

1) Remove the screw caps on each end of the connector.

Avoid touching the ends of the connector and syringe tips, to prevent contamination

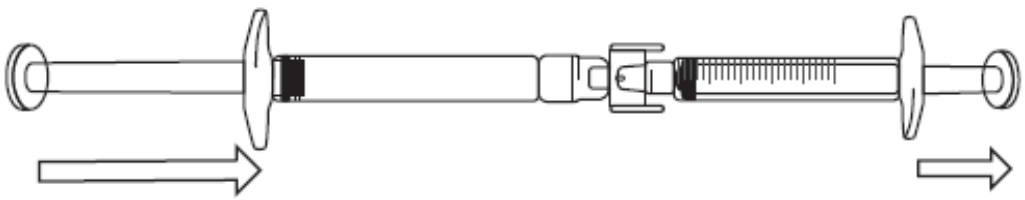
2) Screw the connector onto the pre-filled syringe.

3) Attach the graduated syringe to the other end of the connector ensuring that both connections fit securely.

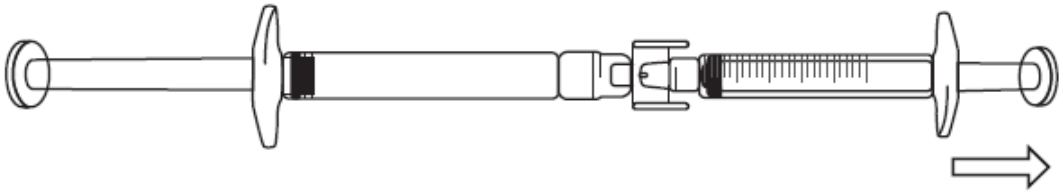


Transferring the icatibant solution to the graduated syringe:

1) To start transfer of icatibant solution, push the pre-filled syringe plunger (on far left of below image).



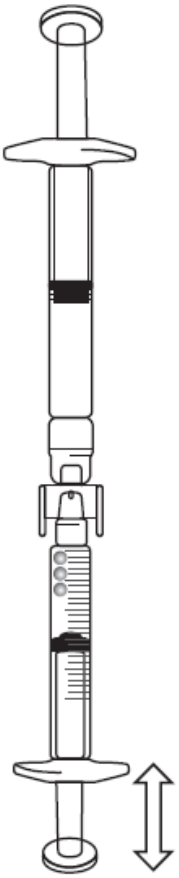
2) If the icatibant solution does not begin to transfer to the graduated syringe, pull slightly on the graduated syringe plunger until the icatibant solution starts to flow into the graduated syringe (see below image).



3) Continue to push on the pre-filled syringe plunger until the required injection volume (dose) is transferred to the graduated syringe. Refer to table 1 for dosage information.

If there is air in the graduated syringe:

- Turn the connected syringes so that the pre-filled syringe is on top (see below image).

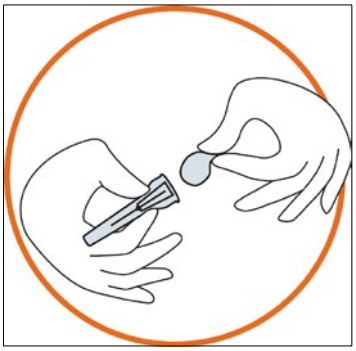


- Push the plunger of the graduated syringe so that any air is transferred back into the pre-filled syringe (this step may need to be repeated several times).
- Withdraw the required volume of icatibant solution.

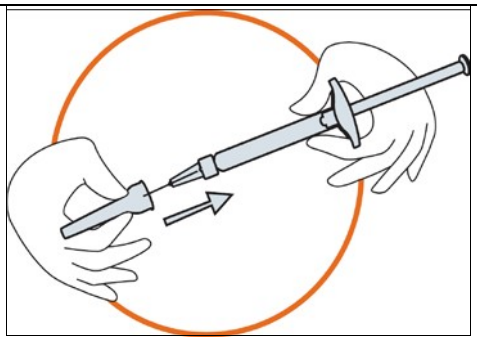
4) Remove the pre-filled syringe and connector from the graduated syringe.

5) Discard the pre-filled syringe and connector into the sharps container.

2b) Preparing the syringe and needle for injection:
All patients (adults, adolescents and children)

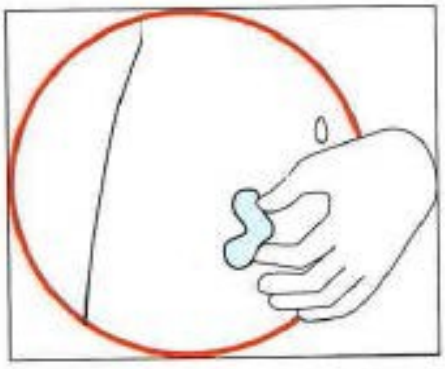


- Remove the needle cap from the blister.
- Remove the seal from the needle cap (the needle should be still in the needle cap).



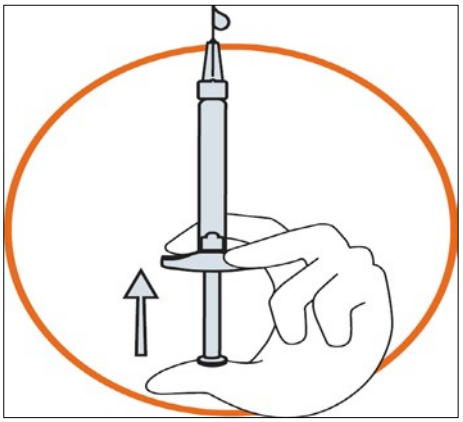
- Grip the syringe firmly. Carefully attach the needle to the syringe containing the colourless solution.
- Screw the syringe on the needle still fixed in the needle cap.
- Remove the needle from the needle cap by pulling the syringe. Do not pull up on the plunger.
- The syringe is now ready for injection.

3) Preparing the injection site

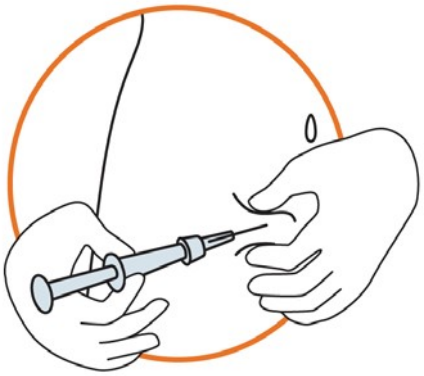


- Choose the injection site. The injection site should be a skin fold on your abdomen approximately 5-10 cm (2-4 inches) below your navel on either side. This area should be at least 5 cm (2 inches) away from any scars. Do not choose an area that is bruised, swollen, or painful.
- Clean the injection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

4) Injecting the solution

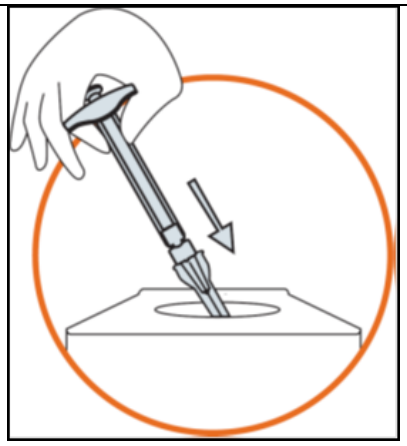


- Hold the syringe in one hand between two fingers with your thumb at the bottom of the plunger.
- Make sure that there is no air bubble in the syringe by pressing the plunger until the first drop appears on the tip of the needle.



- 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 Icatibant Accord 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.

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

Common (may affect up to 1 in 10 people):
Feeling sick
Headache
Dizziness
Fever
Itching
Rash
Skin redness
Abnormal liver function test

Not known (frequency cannot be estimated from the available data):
Hives (urticaria)

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

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. 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 Icatibant Accord

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.

This medicine does not require any special temperature storage conditions.
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 Icatibant Accord contains

The active substance is icatibant. Each pre-filled syringe of 3 ml contains icatibant acetate equivalent to 30 mg of icatibant. Each ml of the solution contains 10 mg of icatibant. The other ingredients are sodium chloride, glacial acetic acid, sodium hydroxide and water for injection.

What Icatibant Accord looks like and contents of the pack

Icatibant Accord is presented as a clear, colourless solution , practically free from foreign particles in a pre-filled syringe out of glass of 3 ml. Hypodermic needle is included in the pack.

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

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Accord Healthcare S.L.U.
World Trade Center,
Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona, Spain

Manufacturer:
Accord Healthcare Polska Sp.z o.o.
ul. Lutomierska 50,
95-200 Pabianice
Poland

Or
Accord Healthcare B.V.
Winthontlaan 200, 3526KV Utrecht
The Netherlands

This leaflet was last revised in {MM/YYYY}.

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