20 May 2021
EMA/306744/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Icatibant Accord

International non-proprietary name: icatibant

Procedure No. EMEA/H/C/005083/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACE : Angiotensin Converting Enzyme

AE : Adverse events

AE : Angioedema

Al : Aluminium

ALT : alanine Transaminase

API : Active Pharmaceutical Ingredient

APP : Amino Peptidase P

ASMF : Active Substance Master File = Drug Master File

AST : Aspartate Transaminase

BK : Bradykinin

Cmax : Maximum measured concentration of drug in plasma

CYP : Cytochrome P

DPPIV : Dipeptidyl peptidase IV

FAST-1 : For Angioedema Subcutaneous Treatment (FAST)- Phase-1 study

FAST-2 : For Angioedema Subcutaneous Treatment (FAST)- Phase-2 study

FAST-3 : For Angioedema Subcutaneous Treatment (FAST)- Phase-3 study

Fmoc : Fluorenylmethoxycarbonyl

FT-IR : Fourrier Transform Infrared Spectroscopy

GC-MS : Gas chromatography mass spectrometry

HAE : Hereditary Angioedema

HAE-C1Inh : Hereditary Angioedema with C1 esterase enzyme inhibitor deficiency

HCPs : Healthcare Professionals

IOS : Icatibant Outcome Survey

IR : Infrared

ITT : Intent-to-treat

MAA : Marketing Authorisation Application

MS : Mass Spectrometry

NLT : Not less than

NMR : Nuclear Magnetic Resonance

OLE : Open Label Extension Phase

PE : Polyethylene

PET : Polyethylene terephthalate

Ph. Eur. : European Pharmacopoeia

SC : Subcutaneous

SPPS : solid-phase peptide synthesis

tBu : *tert*-butyloxycarbonyl

Tmax : Time to reach the maximum concentration of drug in plasma

UV : Ultraviolet

Vss : Volume of distribution at steady state

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 24 July 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Icatibant Accord, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 31 May 2018.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

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.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data, a biowaiver for bioequivalence study with the reference medicinal product Firazyr instead of non-clinical and clinical data unless justified otherwise.

The chosen reference product is: Firazyr

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 6, 8 or 10 years in the EEA:

- Product name, strength, pharmaceutical form: Firazyr solution for injection in pre-filled syringe 30mg/3ml (10mg/ml).
- Marketing authorisation holder: Shire Pharmaceuticals Ireland Limited
- Date of authorisation: 11/07/2008
- Marketing authorisation granted by Union
- Marketing authorisation number: EU/1/08/461

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Firazyr solution for injection in pre-filled syringe 30mg/3ml (10mg/ml).
- Marketing authorisation holder: Shire Pharmaceuticals Ireland Limited

- Date of authorisation: 11/07/2008
- Marketing authorisation granted by Union
- Marketing authorisation number: EU/1/08/461

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and appointed by the CHMP were:

Rapporteur: Alar Irs

The appointed co-rapporteur had no such prominent role in Scientific advice relevant for the indication subject to the present application.

The application was received by the EMA on	24 July 2020
The procedure started on	13 August 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	4 November 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	16 November 2020
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC members on	27 November 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	10 December 2020
The applicant submitted the responses to the CHMP consolidated List of	02 March 2021

Questions on	
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	26 April 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	06 May 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the to the List of Questions to all CHMP members on	13 May 2021
The CHMP adopted a report on similarity of icatibant with Takzhyro and Orladeyo (Appendix 1)	20 May 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Icatibant Accord on	20 May 2021

2. Scientific discussion

2.1. Quality aspects

2.1.1. Introduction

The finished product is presented as solution for injection containing 30 mg of icatibant (as acetate) as the active substance in 3 mL solution (10 mg/mL).

Other ingredients are: sodium chloride, sodium hydroxide, glacial acetic acid and water for injection.

The product is available in a pre-filled syringe (type I glass) with plunger stopper (bromobutyl coated with fluorocarbon polymer) as described in section 6.5 of the SmPC. A 3 mL syringe is used and a hypodermic needle (25 G; 16 mm) is included in the pack. The product is intended for single administration.

2.1.2. Active substance

General information

The information on icatibant was provided in the form of an active substance master file (ASMF).

Icatibant is a synthetic decapeptide. It consists of ten amino acids in the following sequence: H-D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-D-Tic-Oic-Arg-OH.

The chemical name of icatibant acetate is D-arginyl-L-arginyl-L-prolyl-L[(4R)-4-hydroxyprolyl]-glycyl-L[3-(2-thienyl)Alanyl]-L-seryl-D-(1,2,3,4-tetrahydroisoquinolin-3-ylcarbonyl)-L[(3as,7as)octahydroindol-2-ylcarbonyl]-L-arginine, acetate salt corresponding to the molecular formula $C_{59}H_{89}N_{19}O_{13}S$. It has a relative molecular mass of 1304.52 g/mol and the following structure:

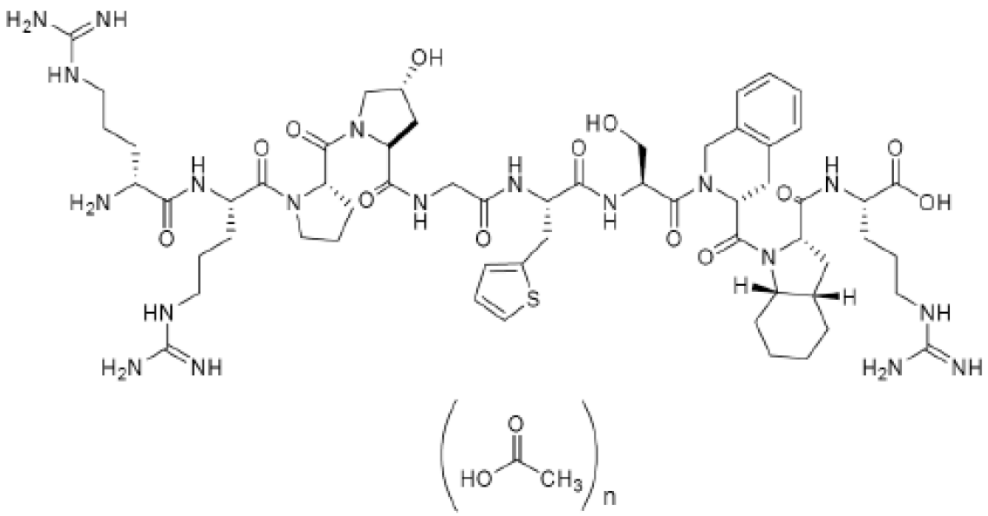

Figure 1: active substance structure

The chemical structure of icatibant was elucidated by various analytical techniques and found satisfactory.

The active substance is a white or off-white powder in amorphous form. It is optically active due to the presence of chiral centres in the amino acids. It is freely soluble in water and hygroscopic by nature. Optical rotation is routinely controlled as part of the active substance specification.

Solid state properties of the active substance such as particle size or potential changes in polymorphic form are not critical since the active substance is dissolved in the finished product (solution for injection).

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and was considered satisfactory.

The active substance in produced by one manufacturer.

Icatibant acetate is synthesised in three main steps using commercially available well-defined starting materials with acceptable specifications.

The designation of the starting materials is in line with ICH Q11 and its Q&A document.

Acceptable limits for impurities (specified, unspecified and total impurities) in the starting materials have been established. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The optical purity of amino acid derivatives and peptides has been investigated to demonstrate that racemisation does not occur.

Sufficient data has been presented to confirm comparability to the reference product Firazyr.

No genotoxic or potentially genotoxic impurities were identified.

All solvents and reagents used throughout the manufacture are commonly used for peptide synthesis.

Carry-over of residual solvents as well as Class 1 solvents which could be contaminants in other solvents has been studied in line with ICH Q3C and CPMP/ICH/283/95.

The active substance is packaged in a high-density polyethylene (HDPE) bottle. The primary packaging material complies with Ph. Eur. chapter 3.2.2 on plastic containers.

Specification

The active substance specification includes tests for: appearance, identity (MS, HPLC, IR), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), specific optical rotation (USP), colour & clarity of solution in water (USP), solubility in water (USP), pH (USP), bacterial endotoxins (USP) and microbial enumeration (USP) and absence of *E. coli* (USP).

Limits for impurities are set in line with ICH Q3A. The limit for total impurities is considered acceptable based on batch analysis data.

The absence of elemental impurities as per ICH Q3D Option 1 has been demonstrated.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay testing and the three working standards for impurity testing has been presented.

Batch analysis data of three commercial-scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data of active substance, which is of commercial scale and manufactured by the proposed manufacturer, stored in packaging representative of the commercial packaging for up to 48 months under long term conditions and for up to 6 months under accelerated conditions according to the ICH guidelines, were provided. No significant changes were observed, and the results were within specifications.

The parameters tested are the same as for release. The analytical methods used were the same as for release and were stability indicating.

Forced degradation studies have been performed and the active substance degrades under conditions of light, high temperature and humidity as well as acidic, alkali and oxidative conditions. An increase in impurity levels was observed.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable under the proposed storage conditions (store in tight, light resistant containers, store in freezer (-20±5°C)). The stability results justify the proposed retest period in the proposed container.

2.1.3. Finished medicinal product

Description of the product and pharmaceutical development

The finished product icatibant, solution for injection, 30 mg/3 mL is presented as a clear, colourless solution in a clear glass pre-filled syringe (PFS).

The purpose of pharmaceutical development was to develop a generic formulation of icatibant, solution for injection, 30 mg/3 mL which is equivalent to the reference product Firazyr.

The generic product has the same pharmaceutical form, the same qualitative and quantitative composition in terms of the active substance and the same qualitative composition in terms of excipients as the reference product Firazyr (solution for injection in a pre-filled syringe). Both the generic and the reference product contain the active substance in the acetate form.

Since the finished product is a solution, solid-state properties of the active substance have no impact on performance of the finished product.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Sufficient information related to the development of the finished product has been provided. Comparative structural and performance investigations confirm the similarity of the generic product with the reference product.

The choice of the excipients has been justified, and their functions explained. The compatibility of excipients with the active substances was proven by stability studies.

No bioequivalence study was required since the finished product is a parenteral dosage form and is administered as an aqueous solution containing the same active substance in the same concentration as the reference product.

Sufficient information related to manufacturing process development has been provided. Several studies have been performed to optimise the manufacturing process of the finished product. The process is robust and suitable for industrial manufacturing.

The materials involved in the manufacturing process of the final product have been described in sufficient detail and their compatibility with the finished product has been adequately demonstrated.

The microbial attributes for the finished product are sufficiently monitored by sterility and bacterial endotoxins testing in the finished product at release and during the stability studies. Additional assurance of the microbiological quality of the product is provided by container closure integrity testing.

The primary packaging for the 3 mL of solution is a 3 mL pre-filled syringe (type I glass) with plunger stopper (bromobutyl coated with fluorocarbon polymer). The material complies with Ph. Eur. and EC requirements. The proposed container closure system is the same as used for the reference product and considered adequate. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

A hypodermic needle (25 G; 16 mm) is included in the pack. The injection needle is a non-integral medical device, complies with Medical Devices Directive 93/42/EEC and has CE mark certification. Icatibant Accord is indicated for adults, adolescents and children aged 2 years and older. No graduation is needed on the syringes as the complete content of the syringes is injected for adult patients. When used in the paediatric population, where the dose is less than 30 mg (3 ml) based on body weight, additional equipment (connector, 3 ml graduated syringe) is required to extract the appropriate dose. This information included in the SmPC section 6.6 and is in line with the SmPC of the reference product.

Information has been provided on the extractables and leachables study. All leachables were found below the Analytical Evaluation Threshold.

Manufacture of the product and process controls

The manufacturing process consists of three main steps: mixing of the active substance and excipients with pH adjustment, filtration and terminal sterilisation. The process is considered to be a standard manufacturing process.

The finished product is terminally sterilised in the final container by heat using the reference condition of the European Pharmacopeia for steam sterilisation.

Validation of the manufacturing process has been completed on three commercial scale batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, identification (HPLC), colour of solution (Ph. Eur.), clarity of solution (Ph. Eur.), pH (Ph. Eur.), extractable volume (Ph. Eur.), impurities (HPLC), assay (HPLC), particulate contamination (Ph. Eur.), bacterial endotoxins (Ph. Eur.), sterility (Ph. Eur.), osmolality (Ph. Eur.), break loose force (in house), glide force (in house) and uniformity of dosage units (Ph. Eur.).

The proposed specifications are compliant with ICH Q6A and cover appropriate parameters for this dosage form.

The proposed limits for the impurities have been appropriately justified.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the “Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products” (EMA/409815/2020) and the “Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products” (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines or reference is made to the relevant Ph. Eur. chapters.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data for several commercial scale batches of the finished product used in process validation and stability studies have been provided confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from several production-scale batches of finished product stored for up to 24 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing. The analytical procedures used are stability indicating. No significant change was observed, and all the results met the established criteria. Overall, the tested parameters are considered adequate to indicate stability sufficiently.

In addition, one batches was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The product was found not to be sensitive to light in clear glass syringes.

The expiry date of the product is calculated in accordance with the Note for Guidance on Start of the Shelf-life of the Finished Dosage Form (CPMP/QWP/072/96).

Based on available stability data, the proposed shelf-life of 24 months as stated in the SmPC (section 6.3) is acceptable. The medicinal product does not require any special storage conditions. Considering the finished product is in glass containers and to be in line with products on the market, the supplementary warning “Do not freeze” has been included in the SmPC (section 6.4).

Adventitious agents

No excipients derived from animal or human origin have been used.

2.1.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.1.6. Recommendations for future quality development

Not applicable.

2.2. Non-clinical aspects

2.2.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. Pharmacodynamic, pharmacokinetic and toxicological properties of icatibant are well known. As icatibant is a well-known active substance, overview based on mostly literature review is, thus, appropriate. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product.

The applicant provided a revised Module 4 with inclusion of the toxicology study according to the eCTD structure, and a revised non-clinical overview, with inclusion of more detailed information on the performed toxicological study. The impurity profile has been discussed and the data provided is considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.2.2. Ecotoxicity/environmental risk assessment

The applicant has provided updated information related to environmental risk assessment. The presented data allows the conclusion that the medicinal product is unlikely to represent a risk for the environment. This was justified by the applicant as the introduction of Icatibant Accord manufactured by Accord Healthcare S.L.U. is considered unlikely to result in any significant increase in the combined sales volumes for all icatibant containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.2.3. Discussion on non-clinical aspects

There are no objections to approval of Icatibant Accord from a non-clinical point of view.

2.2.4. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Icatibant Accord and justifications that icatibant does not differ in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional non-clinical studies were not considered necessary.

2.3. Clinical aspects

2.3.1. Introduction

This is an application for a solution for injection containing icatibant. This application concerns a generic version of icatibant acetate solution for injection. The reference product Firazyr 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.

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.

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

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

GCP

Not applicable

Exemption

The applicant provided a table summarising the qualitative composition of their product with the reference medicinal product Firazyr.

The aqueous Icatibant formulation is administered subcutaneously preferably in the abdominal area. The concentration of the active substance is the same and the same excipients are used as for the reference product.

Table 1: Qualitative comparison of applicant's product against European reference product Firazyr® Icatibant (as acetate) 30 mg injection in pre-filled syringe.

Product	**Applicant's formulation**	**EU reference product**
	Icatibant Injection, 30 mg	Firazyr® 30 mg
MAH	Accord Healthcare S.L.U.	Shire Pharmaceuticals Ireland Limited
Dosage form	Solution for injection in pre-filled syringe	Solution for injection in pre-filled syringe
Strength	30 mg	30 mg
API	Icatibant (30 mg/3 mL)	Icatibant (30 mg/3 mL)
Ingredients	Sodium Chloride	Sodium Chloride
	Sodium hydroxide	Sodium hydroxide
	Acetic acid, glacial	Acetic acid, glacial
	Water for injections	Water for injections

According to the Note for Guidance on the "Investigation of bioavailability and bioequivalence" (CPMP/EWP/QWP/1401/98) no additional studies are considered necessary to confirm the bioequivalence with the reference medicinal product. The waiver justification provided by the applicant is acceptable.

Clinical studies

There are no bioequivalence studies submitted with this application

No new studies were presented and no such studies are required for this application.

2.3.2. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.3.3. Discussion on clinical aspects

The Art. 10(1) application is justified as this medicinal product, for which the application is made, has the same strength (30 mg), the same quality composition of the active substance (Icatibant acetate) and the same

pharmaceutical form (solution for injection in pre-filled syringe) as well as the indication, route of administration and patient population are the same, as the reference product Firazyr 30mg/3ml solution for injection in pre-filled syringe by Shire Pharmaceuticals Ireland Limited, approved since 2008-07-11 via central procedure (EMEA/H/C/000899).

The applicant provided a table summarising the qualitative composition of their product with the reference medicinal product Firazyr.

According to the Note for Guidance on the "Investigation of bioavailability and bioequivalence" (CPMP/EWP/QWP/1401/98) no additional studies are considered necessary to confirm the bioequivalence with the reference medicinal product. The waiver justification provided by the applicant is acceptable. The proposed formulation is administered by parenteral route and has been developed is to the reference product and composition and physicochemical parameters are comparable.

A summary of the literature with regard to clinical data of Icatibant Accord and justifications that the active substance does not differ in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional clinical studies were not considered necessary.

2.3.4. Conclusions on clinical aspects

A summary of the literature with regard to clinical data of Icatibant Accord and justifications that the active substance does not differ in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional clinical studies were not considered necessary. The product information is adequate and reflects the scientific information of the reference product.

2.4. Risk management plan

Safety concerns

Table 2: Summary of safety concerns RMP version 1.1 final sign off 16 -Dec-2020

Summary of safety concerns	
Important identified risks	Injection site reactions
Important potential risks	Deterioration of cardiac function under ischaemic conditions due to bradykinin antagonism Partial bradykinin agonism (excluding injection site reactions) Antigenicity manifesting as drug hypersensitivity and lack of efficacy Lack of efficacy Medication errors
Missing information	Use in pregnant and lactating women Use in children below 2 years of age

Pharmacovigilance plan

No additional pharmacovigilance activities have been proposed or requested.

Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection are deemed sufficient.

Overall conclusions on the Pharmacovigilance Plan

Routine pharmacovigilance remains sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

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

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.1 is acceptable.

2.5. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports 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.

2.6. Product information

2.6.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Firazyr). The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of icatibant acetate solution for injection. The reference product Firazyr 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.

No nonclinical studies have been provided for this application apart from impurity toxicity studies and an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Icatibant Accord is favourable in the following indication:

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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports 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.

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 the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Similarity

With reference to Article 8 of Regulation (EC) No 141/2000, Icatibant Accord (Icatibant) is considered not similar to the medicinal product Takhzyro within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.