COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Kisilea 30 mg solution for injection, in prefilled syringe

(icatibant acetate)

(NL/H/5433/001/DC)

Date: 30 March 2022

This module reflects the scientific discussion for the approval of Kisilea. The procedure was finalised at 20 December 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Kisilea 30 mg solution for injection, in prefilled syringe, from Viatris Limited.

The product 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.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Firazyr 30 mg solution for injection in pre-filled syringe which has been registered in the European Union (EU) since 11 July 2008 by Shire Pharmaceuticals Ireland Limited (EU/1/08/461/ 001 & 002) (original product).

The concerned member states (CMS) involved in this procedure were Germany, Denmark, Finland, France, Italy, Norway and Sweden.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

Assessment of similarity with authorised orphan medicinal product(s) under market exclusivity: Potential similarity with orphan medicinal products

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Firazyr 30 mg solution for injection in pre-filled syringe, authorised in community since 11 July 2008, with Shire Pharmaceuticals Ireland Limited as marketing authorisation holder. Firazyr had been granted orphan market exclusivity for "treatment of angioedema" (based on designation EU/3/03/133). The ten year market exclusivity started on 15th July 2008, with two additional years of market exclusivity as paediatric reward granted on 23rd Oct 2017. The orphan market exclusivity expired on 15th July 2020.

Furthermore, having considered the arguments presented by the MAH and with reference to Article 8 of Regulation (EC) No 141/2000, Kisilea is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Takhzyro. Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Takhzyro in the treatment of hereditary angioedema (HAE) does not prevent the granting of the marketing authorisation of Kisilea. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

There is one orphan designation: EU/3/15/1551. This product with Orphan designation EU/3/18/2028 (Orladeyo) is no longer an orphan medicine. It was originally designated an orphan medicine on 27 June 2018. The product was withdrawn from the Union Register of

orphan medicinal products by the European Commission in March 2021 upon request of the marketing authorisation holder at the time of the granting of a marketing authorisation.

II. QUALITY ASPECTS

II.1 Introduction

Kisilea is a clear and colourless solution with a pH of approximately 5.5 and osmolarity of approximately 300 mOsm/kg.

Each pre-filled syringe of 3 ml contains as active substance 30 mg of icatibant. Each ml of the solution contains 10 mg of icatibant.

The solution is packed in glass pre-filled syringes and is supplied with a hypodermic needle.

The excipients are sodium chloride, acetic acid – glacial (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

II.2 Drug Substance

The active substance is icatibant acetate, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). The drug substance is a white to almost white amorphous powder, which is freely soluble in water. Icatibant acetate is amorphous and exhibits optical isomerism as it contains multiple chiral centers. Polymorphism is not relevant as the active substance is used in solution.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

<u>Manufacturing process</u>
The synthesis of icatibant acetate is executed in three stages and includes the preparation of the crude active substance, the pure active substance and then the final active substance. No class 1 solvents or heavy metal catalysts are used during the manufacturing process. All solvents used during the API manufacturing process are controlled in the drug substance specification. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. The specification contains tests for appearance, solubility, identification, water content (KF), specific optical rotation, related substances, assay, residual solvents, bacterial endotoxins and microbiological limit test. Batch analytical data demonstrating compliance with this specification have been provided for six commercial scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three production scaled batches stored at 5°C ± 3°C (48 months) and -20°C ± 5°C (36 months) in accordance with applicable European guidelines demonstrating the stability of the active substance for 36 months when stored in polyethylene bags and containers. No significant changes and no trends are observed in any of the parameters studied. Based on the data submitted, a retest period could be granted of 36 months when stored in a well closed container protected from moisture at below -20±5°C.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The proposed drug product is full copy of the reference product Firazyr, as it contains the same amounts of the same active substance and excipients, has the same physical-chemical characteristics as pH and osmolality, comparable purity of the active substance, aggregation of molecules (none) and also the packaging components, including needle for subcutaneous administration, are similar. Suitable development studies have been conducted to choose and justify the specific aspects of the drug product manufacturing process and its control. The choice for terminal sterilization process is appropriate. Suitability of the packaging components has been substantiated.

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines. The manufacturing process is a standard, straightforward process of weighing, dissolution, mixing, filtration, filling in syringes and terminal sterilisation. Process validation data on the product have been presented for three full scale batches in accordance with the relevant European guidelines.

Control of excipients
The excipients are usual for a solution for injection. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, color and clarity of solution, pH, osmolality, extractable volume, uniformity of dosage units by mass variation, assay, particulate contamination, related substances, bacterial endotoxins, sterility, break loose force test, glide force test, and container closure integrity test. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three full scale batches from the proposed production site has been provided, demonstrating compliance with the specification. Suitable risk evaluations on elemental impurities and on nitrosamine impurities have been provided.

Stability of drug product

Stability data on the product have been provided for three batches covering six months accelerated (40 ± 2ºC/75% ± 5% RH), 12 months intermediate (30°C ± 2°C / 65% ± 5% RH) and 24 months long term (25ºC ± 2ºC/60% ± 5% RH) storage in accordance with applicable European guidelines demonstrating the stability of the product for 24 months. On basis of the data submitted, a shelf life was granted of 24 months with the labelled storage conditions: 'do not store above 30°C. Do not freeze'.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Kisilea has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Kisilea is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Firazyr which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Icatibant acetate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted no bioequivalence studies, the reason for this will be explained in section IV.2.

IV.2 Pharmacokinetics

Kisilea 30 mg solution for injection, in prefilled syringe is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Kisilea 30 mg is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

Biowaiver

A clinical trial is not required for this application, since the product of the MAH is a parenteral solution for subcutaneous use, and is of the same type (aqueous solution), contains the same concentration of Icatibant acetate and the same excipients as Firazyr 30 mg solution for injection. Moreover, the subcutaneous injection is not intended as a modified release dosage form and has not a special formulation (e.g. liposomal, micellar and emulsion dosage form).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Kisilea.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• Injection site reactions
Important potential risks	• Deterioration of cardiac function under ischaemic conditions due to bradykinin antagonism • Partial bradykinin antagonism (excluding injection site reactions) • Antigenicity manifesting as drug hypersensitivity and lack of efficacy • Lack of efficacy • Medication errors • Effect on reproductive hormone levels in pubertal/post-pubertal children
Missing information	• Use in pregnant and lactating women • Use in children below two years of age

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Firazyr 30 mg solution for injection. No new clinical studies were conducted. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to the PL of the centrally authorized Firazyr 30 mg solution for injection (EU/1/08/461/ 001 & 002) as the parent leaflet for the content analysis and the style and design aspects with Itraconazol Aurobindo 100 mg, hard capsules

(RVG 107049). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Kisilea 30 mg solution for injection, in prefilled syringe has a proven chemical-pharmaceutical quality and is a generic form of Firazyr 30 mg solution for injection. Firazyr is a well-known medicinal product with an established favourable efficacy and safety profile.

Therapeutic equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of *in vitro* studies on the relevant quality attributes. A biowaiver has been granted.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Kisilea with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 December 2021.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse