

Public Assessment Report

Scientific discussion

Ivacaftor Galenika (ivacaftor)

SE/H/2670/01/DC

This module reflects the scientific discussion for the approval of Ivacaftor Galenika. The procedure was finalised at 2026-01-21. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Ivacaftor Galenika, 150 mg, Film-coated tablet.

The active substance is ivacaftor. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

The active ingredient is ivacaftor, a CFTR (cystic fibrosis transmembrane conductance regulator) modulator. It increases the channel activity of the CFTR protein located at the cell surface through increased gating activity, resulting in increased chloride transport.

The product is indicated for the treatment of patients with cystic fibrosis who have certain listed CFTR mutations.

II.2 General comments on the submitted dossier

The application for Ivacaftor Galenika, 150 mg, film-coated tablet, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and with concerned member states (CMS) as follows:

SE/H/2670/01/DC: HR, HU, SI

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Kalydeco, 150 mg, film-coated tablet authorised in the Union since 2012, with Vertex Pharmaceuticals (Ireland) Limited as marketing authorisation holder.

The reference product used in the bioequivalence study is Kalydeco, 150 mg, film-coated tablet from Germany with Vertex Pharmaceuticals (Ireland) Limited as marketing authorisation holder.

Potential similarity with orphan medicinal products

Having considered the arguments presented by the applicant and with reference to Article 8 of Regulation (EC) No 141/2000, Ivacaftor Galenika is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Symkevi, Kaftrio and Alyftrek.

Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Symkevi, Kaftrio and Alyftrek in the treatment of cystic fibrosis, does not prevent the granting of the marketing authorisation of Ivacaftor Galenika. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer

authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance

Regarding the statement on GMP for the active substance an acceptable statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and of the batch release situated in the EU.

GCP

A statement on the application of appropriate GCP standards in the submitted study has been provided. The clinical and the bioanalytical facilities were inspected by the FDA and EU Authorities (AGES, DKMA, CBG) in 2022, without any critical findings. No issues regarding GCP have been identified. No inspection of the submitted bioequivalence studies is needed.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

The structure of the drug substance has been adequately proven, and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described, and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

Drug Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology

Pharmacodynamic, pharmacokinetic and toxicological properties of ivacaftor are well known. As ivacaftor is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)

The Applicant has provided an ERA for their product following the advice for generic products described in the current ERA guideline (EMA/CHMP/SWP/4447/00 Rev. 1- Corr.*, 22 Aug 2024). Kaftrio and Kalydeco (both marketed by Vertex Pharmaceuticals (Ireland) Limited) were identified as reference products for the ivacaftor ERA, with the latest ERA approved in 2020. Letter of Access to previously conducted ERA studies was denied by the originator MAH as evidenced in the submitted correspondence.

The Applicant has calculated PEC_{sw} with default F_{pen} for ivacaftor in their product and obtained the value of 1.5 µg/L. To calculate refined F_{pen}, prevalence from Italy, France and Belgium, as the concerned EU member states with the highest prevalence values (according to the submitted reports from ECFSR and ICFR), was applied and obtained PEC_{sw,refined} was 0.015 µg/L. This value is accepted, and Phase II studies are triggered.

For the Phase II studies, the Applicant refers to the reference product ERA. All studies that are required according to the current ERA guideline have been performed. Secondary poisoning and groundwater assessments are not warranted, while soil assessment is triggered and has been conducted for the reference product. No risk for the environment has been identified in any of the compartments for the reference product.

No increase in environmental exposure is expected with this generic product as it will be used in the same indications as the original product Kalydeco, containing only ivacaftor, and no change in the disease prevalence is expected.

Definitive PBT/vPvB assessment was triggered for the reference product since logK_{ow} > 4.5.

Ivacaftor was determined not to be PBT/vPvP.

Altogether, the ERA of the reference product is considered complete and valid for the present product.

In conclusion, the present ivacaftor product does not pose risk for environment.

III.3 Clinical aspects

Pharmacokinetics

To support the marketing authorisation application the applicant has conducted one single-dose bioequivalence study comparing Ivacaftor with the reference product Kalydeco.

Pharmacokinetic properties of the active substance

Absorption: Following multiple oral dose administrations of ivacaftor, the exposure of ivacaftor generally increased with dose from 25 mg every 12 hours to 450 mg every 12 hours. When given with fat-containing food, the exposure of ivacaftor increased approximately 2.5- to 4-fold. Therefore, ivacaftor, administered as monotherapy should be administered with fat-containing food. The median (range) t_{max} is approximately 4.0 (3.0; 6.0) hours in the fed state.

Linearity: The pharmacokinetics of ivacaftor are generally linear with respect to time or dose ranging from 25 mg to 250 mg.

Elimination: The apparent terminal half-life was approximately 12 hours following a single dose in the fed state.

Study 2853

Methods

This was a single-dose, two-way crossover study conducted in 42 healthy volunteers, comparing Ivacaftor, 150 mg, film-coated tablet with Kalydeco, 150 mg, film-coated tablet under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 48 hours post-dose. Plasma concentrations of ivacaftor were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max} . The study was conducted between 17th November 2023 and 4th January 2024.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean $\pm$ SD, t_{max} median, range) for ivacaftor, n=41.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	9357.43 $\pm$ 3279.26	791.89 $\pm$ 262.24	4.67 (1.50 -10.00)
Reference	8899.11 $\pm$ 2985.72	764.97 $\pm$ 302.00	4.67 (1.50 -7.07)
*Ratio (90% CI)	105.31 (99.66 - 111.27)	105.26 (96.63 - 114.66)	-
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration			

*calculated based on ln-transformed data

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Discussion and overall conclusion

The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence study (2853), Ivacaftor 150 mg film-coated tablet is considered bioequivalent with Kalydeco 150 mg film-coated tablet.

Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Bioequivalence with the originator product has been demonstrated, and additional data is therefore not necessary.

Pharmacovigilance system

Proposed MAH -SE/H/2670/01/DC: Galenika International Kft.

The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

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 Ivacaftor Galenika.

Part II Safety specification

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Hepatotoxicity
	• Cataract
Missing information	• Use in pregnant and lactating women
	• Indicated use in children aged less than 6 years

The safety specification is aligned with that of the reference product and is thus endorsed.

Part III Pharmacovigilance Plan

In line with the reference product, the Applicant proposes the implementation of a specific adverse reaction follow-up questionnaire to obtain structured information on the following safety concern:

- Use in pregnant and lactating women

The specific follow-up form is provided in Annex 4 of the RMP.

Part V Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP

The Summary of the RMP is endorsed.

Conclusion RMP assessment

The MAH has satisfactorily responded to the questions raised and updated the RMP accordingly.

SE/H/2670/01/DC: The submitted Risk Management Plans for Ivacaftor Galenika, version 0.4 dated 2026.01.08, is considered acceptable.

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 RMS;
- 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)

Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.>

Common renewal date

The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Ivacaftor Galenika, is found adequate. There are no objections to approval of Ivacaftor Galenika, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-