LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Qulventra
(ivacaftor)

SE/H/2756/001-002/DC

This module reflects the scientific discussion for the approval of Qulventra. The procedure was finalised at 2026-05-27. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.

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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 Qulventra 75 mg, 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 indication is for cystic fibrosis patients who have certain listed CFTR mutations.

II.2 General comments on the submitted dossier

The application for Qulventra, 75 mg, 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 DE, EL, ES, FR, MT, RO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Kalydeco, 75 mg, film-coated tablets authorised in 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 tablets from DE 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, Qulventra is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Symkevi and Kaftrio.

Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Symkevi in the treatment of patients with cystic fibrosis (CF) aged 6 years and older who are homozygous for the F508del mutation or who are heterozygous for the F508del mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T, does not prevent the granting of the marketing authorisation of Qulventra. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Kaftrio, Kaftrio tablets are indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (see section 5.1)

does not prevent the granting of the marketing authorisation of Qulventra. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application

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 described. 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 ERA for the present product was conducted according to the latest ERA guideline (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.) following the instructions for generic products. Two products, centrally approved in the EU, Kaftrio and Kalydeco, were used as reference products. The RP ERAs were updated in 2020. According to the current EMEA ERA guideline, no new compartments are triggered for the RP and no new studies are needed, and the previous ERA conclusions remain valid, that ivacaftor does not pose any risk for the environment and is not PBT/vPvB.

Furthermore, patient population for the present product is smaller than the one for all indications included in the Kaftrio's or Kalydeco's ERA. In addition, the product is generic, and as such has the same posology, and administration way as the reference product. Therefore, the environmental exposure to the present product is going to be lower than for the reference product. Since there was no

environmental risk identified for the reference product, it can be concluded that there is no such risk for the present product, either.

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted two bioequivalence studies comparing Ivakaftor, 150 mg, film-coated tablets with the reference product Kalydeco (one in the fed state and one in the fasted state).

Pharmacokinetic properties of the active substance
Absorption: When given with fat- containing food, the exposure of ivacaftor increased approximately 2.5- to 4-fold. Therefore, ivacaftor, 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 C1B04199 (fed state)
Methods
This was a single-dose, two-way crossover study conducted in 60 healthy volunteers (55 completed), comparing Ivakaftor, 150 mg, film-coated tablets with Kalydeco 150 mg, film-coated tablets under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of ivakaftor 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 10th and 29th June 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 ± SD, t_{max} median, range) for ivakaftor, n=55.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**13435 ± 6258**	**859 ± 274**	**4.667 (3.333-7.000)**
Reference	**13628 ± 6043**	**893 ± 286**	**4.667 (3.333-7.000)**
***Ratio (90% CI)**	**98.53% (93.07%-104.32%)**	**96.36% (91.25%-101.75%)**	**-**
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%.

Study C1B05963 (fasted state)

Methods

This was a single-dose, two-way crossover study conducted in 80 healthy volunteers (77 completed), comparing Ivakaftor, 150 mg, film-coated tablets with Kalydeco 150 mg, film-coated tablets under fasted conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of ivakaftor 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 13th and 24th September 2025.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 2 below.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for ivakaftor, n=77.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**5267 ± 3719**	**325 ± 252**	**3.667 (1.667 - 6.000)**
Reference	**5198 ± 3560**	**315 ± 215**	**3.667 (1.333 - 8.000)**
***Ratio (90% CI)**	**103.03% (93.67%-113.32%)**	**99.16% (88.68%-110.89%)**	**-**

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%.

A biowaiver was sought for the additional strength of 75 mg.

Discussion and overall conclusion

The product applied for as well as the reference product is a high-risk product with specific formulation characteristics. According to ICH M13A (EMA/CHMP/ICH/953493/2022), for this type of product both a fasted and a fed study are needed, irrespective of the drug product labelling with regard to food intake. The Applicant originally submitted only a study in the fed state, but an additional study in the fasted state was submitted in response to questions raised.

The performed bioequivalence studies in the fasted and in the fed state and their 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) and ICHM13A, and the provided meal in the fed study can be defined as a high-fat high-calorie meal. The bioanalytical methods were adequately validated. Thus, based on the submitted bioequivalence studies, Ivakaftor, 150 mg, film-coated tablets are considered bioequivalent with Kalydeco 150 mg, film-coated tablets.

Absence of studies with the additional strength of 75 mg is acceptable, as all conditions for biowaiver for additional strength(s), as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr), are fulfilled.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Since bioequivalence with the originator product is demonstrated, additional data is not necessary.

Pharmacovigilance system
Proposed MAH: PharmaPath S.A.

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 Qulventra.

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 less than 6 years

The summary of safety concerns is harmonised with the reference product and is thus endorsed.

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant. Nevertheless, in accordance with the RMP of the reference product, a pregnancy safety information collection form is added as a routine pharmacovigilance activity beyond adverse reactions reporting and signal detection. This is endorsed.

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 submitted Risk Management Plan, **version 0.3 signed 26.03.2026**, 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 products, Qulventra, is found adequate. There are no objections to approval of Qulventra, 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

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Kalydeco 75 mg and 150 mg film-coated tablets, EMEA/H/C/002494 for the content of the package leaflet, and to Apixaban PharmaPath 2.5 mg and 5 mg film-coated tablets, DK/H/3385/001-002/DC for the design/layout of the package leaflet.
The bridging report submitted by the applicant has been found acceptable.

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
-	-	-	-	-	-