LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

# Public Assessment Report
# Scientific discussion

# Ivacaftor STADA Nordic
# (ivacaftor)

# SE/H/2631/01/DC

**This module reflects the scientific discussion for the approval of Ivacaftor STADA Nordic. The procedure was finalised at 2025-05-08. 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 STADA Nordic, 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, which is a CFTR-modulator. It increases the channel activity of 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 Ivacaftor STADA Nordic, 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 the following CMSs as concerned member states (CMS).

| | |
|---|---|
| SE/H/2631/01/DC – Ivacaftor STADA Nordic. | CMS: DE |

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 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 STADA Nordic 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 Ivacaftor STADA Nordic. 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.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturers responsible for manufacture of the finished product and 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 inspection of the submitted bioequivalence studies is needed. No issues regarding GCP have been identified.

# 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, nor does the applicant provide any. Overview based on literature review is, thus, appropriate. The provided nonclinical overview of ivacaftor included public literature for non-clinical pharmacology and pharmacokinetics but was, for toxicology, essentially similar to the Public assessment report for the reference medicinal product Kalydeco® (approved in 2012).

Shortly, ivacaftor is a potentiator of the CFTR protein (causal in the pathogenesis of cystic fibrosis disease). Ivacaftor increases CFTR channel gating (in-vitro) to enhance chloride transport in specified gating mutations with reduced channel-open probability compared to normal CFTR. It should be noted that the in-vitro responses seen in single channel patch clamp experiments using membrane patches from rodent cells expressing mutant CFTR forms do not necessarily correspond to in vivo pharmacodynamic response (e.g., sweat chloride) or clinical benefit. Regarding non-clinical pharmacokinetics (ncPK), ivacaftor generates one major metabolite, M1 (hydroxymethyl-ivacaftor), which is approximately 6x less potent than ivacaftor potentiating CFTR-mediated chloride transport in-vitro. A perinatal exposure study in rat found that, at all ages of exposure (GD19, PND4, PND9 and PND16), entry of ivacaftor into lungs, following either acute or prolonged exposure, was much higher than into brain & CSF. Brain entry appeared higher at earlier ages. Transfer across the placenta in rat – also observed in additional pregnant rat and rabbit studies - and breast milk in rat was estimated to be around ~40% of maternal plasma.

Ivacaftor has been shown to be non-mutagenic and non-clastogenic in the ICH standard battery of genotoxicity tests. It was concluded that ivacaftor was not carcinogenic in lifetime dosing (2 years) studies in mice at 200 mg/kg/day (4 to 7X the human exposure) and rats at 50 mg/kg/day (17 to 31X the human exposure).

Regarding DART aspects, ivacaftor is associated with slight decreases of the seminal vesicle weights in rat, a decrease of overall fertility index and number of pregnancies in females mated with treated males and significant reductions in number of corpora lutea and implantation sites with subsequent reductions in the average litter size and average number of viable embryos per litter in treated females. The No-Observed-Adverse-Effect-Level (NOAEL) for fertility findings provides an animal-to-adult human exposure margin of approximately 4x. Ivacaftor decreased survival and lactation indices and caused a reduction in rat pup body weights. The NOAEL for viability and growth in the offspring provides an animal-to-adult human exposure margin of approximately 3x. Findings of cataracts were observed in juvenile rats dosed from postnatal day 7 through 35 at ivacaftor exposure levels of 0.22x the MRHD based on systemic exposure of ivacaftor and its metabolites when administered as ivacaftor monotherapy.

An elemental impurity and nitrosamine impurity assessment has been conducted.

**Environmental Risk Assessment (ERA)**
The procedure was initiated before 1 Sept 2024 and therefore subject to the 2006 CHMP ERA GL. As such, since Ivacaftor STADA Nordic is a generic product, it is unlikely to lead to an increased exposure to the environment and an environmental risk assessment (Phase I+) is therefore not deemed necessary.

There are no objections to approval of Ivacaftor STADA Nordic from a non-clinical point of view.

## 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 ± 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 ± 3279.26** | **791.89 ± 262.24** | **4.67 (1.50 -10.00)** |
| **Reference** | **8899.11 ± 2985.72** | **764.97 ± 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. Since bioequivalence with the originator product has been demonstrated, additional data is not considered necessary.

**Pharmacovigilance system**

Proposed MAH: STADA Nordic ApS
The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System together with an annex listing all relevant subsidiaries. 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 MAHs have submitted risk management plans, 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 STADA Nordic.

Part II Safety specification

| **List of important risks and missing information** | |
|---|---|
| Important identified risks | • None |
| Important potential risks | • Hepatotoxicity<br>• Cataract |
| Missing information | • Use in pregnant and lactating women<br>• Indicated use in children aged less than 6 years |

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed. In accordance with the reference product’s RMP a pregnancy safety information collection form is added as a routine pharmacovigilance activity beyond adverse reactions reporting and signal detection. Likewise, a follow up questionnaire is in place to gather as much as possible information for spontaneously reported cases of exposure during pregnancy.

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

*SE/H/2631/01/DC:*

The submitted Risk Management Plan, *version 0.3 signed 18/03/2025* is considered acceptable.

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 STADA Nordic, is found adequate. There are no objections to approval of Ivacaftor STADA Nordic, 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

**Post approval commitments**
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 |
|---|---|---|---|---|---|
| - | - | - | - | - | - |