LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Fidaxomicin SUN
(fidaxomicin)

SE/H/2772/001/DC

This module reflects the scientific discussion for the approval of Fidaxomicin SUN. The procedure was finalised at 2026-06-03. 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 Fidaxomicin SUN, 200 mg, film-coated tablet.

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

II. EXECUTIVE SUMMARY

II.1 About the product

Fidaxomicin is a macrocyclic antibiotic that inhibits ribonucleic acid (RNA) synthesis by bacterial RNA polymerase with a narrow spectrum of antibacterial activity.

Sought indication is for the treatment of *Clostridioides difficile* infections (CDI), in adult and paediatric patients with a body weight of at least 12.5 kg. Consideration should be given to official guidelines on the appropriate use of antibacterial agents.

Fidaxomicin has minimal systemic absorption following oral administration, with plasma concentrations of fidaxomicin and its main metabolite (OP-1118) in the ng/mL range at the therapeutic dose. The volume of distribution in humans is unknown, due to very limited absorption of fidaxomicin. Fidaxomicin results in high faecal concentrations (10000× MIC90) with near-100% recovery from faeces.

Fidaxomicin was first approved in the EU in 2011.

II.2 General comments on the submitted dossier

The application for Fidaxomicin SUN, 200 mg, film-coated tablet, is a Hybrid Art. 10(3) 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, ES, FR, IT, PL, RO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Dificlir, 200 mg, film-coated tablet, authorised in the Union since 2011, with Tillotts Pharma GmbH as marketing authorisation holder.

The reference product used in the bioequivalence study is Dificlir, 200 mg, film-coated tablet from Germany with Tillotts Pharma GmbH as marketing authorisation holder.

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 a statement/declaration is provided from the manufacturer(s) 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 studies has been provided. No issues regarding GCP have been identified. The clinical site was inspected by WHO in 2019 and the bioanalytical facilities were inspected by NL/UK in 2017 and by the FDA in 2018 and 2023, without any critical findings. 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
As fidaxomicin is a widely used, well-known active substance, no further studies of

pharmacodynamic, pharmacokinetic and toxicological properties are required, nor does the applicant provide any. An overview based on literature review regarding these properties is, thus, appropriate.

Impurities
The Applicant reports an impurity produced by oxidation of Fidaxomicin resulting in a ketone group instead of hydroxyl group at position 8. A qualification threshold of 0.50% is proposed which is acceptable as the impurity is structurally very similar to the active substance.

Environmental Risk Assessment (ERA)
The Applicant has provided a Letter of commitment to submit an updated, guideline-compliant ERA within 5 years following the granting of the Marketing Authorisation. The updated ERA will include:
• Updated Phase I assessment using either justification of Phase I refinement including the use of recent and representative epidemiological data, or the reference-based approach.
• Updated PBT screening in case applicable.
• Completeness of the ecotoxicological dataset in line with the tailored testing strategy for antibacterial medicinal products.

An updated ERA has been provided to include the above statement.

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted 2 bioequivalence studies comparing Fidaxomicin, 200 mg, tablets with the reference product Dificlir, 200 mg, tablets; one in the fasted state and one in the fed state.

Pharmacokinetic properties of the active substance
The oral bioavailability fidaxomicin is unknown. Following an oral dose of fidaxomicin, maximal plasma concentrations occur at approximately 1.75 hours.

C_{max} for fidaxomicin and its main metabolite OP-1118 were 22% and 33% lower following a high fat meal vs fasting, but the extent of exposure (AUC0-t) was equivalent. There are no restrictions with respect to food in the SmPC of the originator.

Increasing the dose from 200 to 400 mg did not result in a proportional increase in fidaxomicin or OP-1118 C_{max} or AUC_{0-t} values. The terminal half-life is approximately 8-10 hours.

Study FID02524 in the fasted state

Methods
This was a single-dose, fully replicate crossover study conducted in 50 healthy volunteers, comparing Fidaxomicin, 200 mg, tablets with Dificlir, 200 mg, tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of fidaxomicin 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 24th September and 17th October 2024.

Results

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

Figure 1: Fidaxomicin mean plasma concentration – time profile (linear plot)

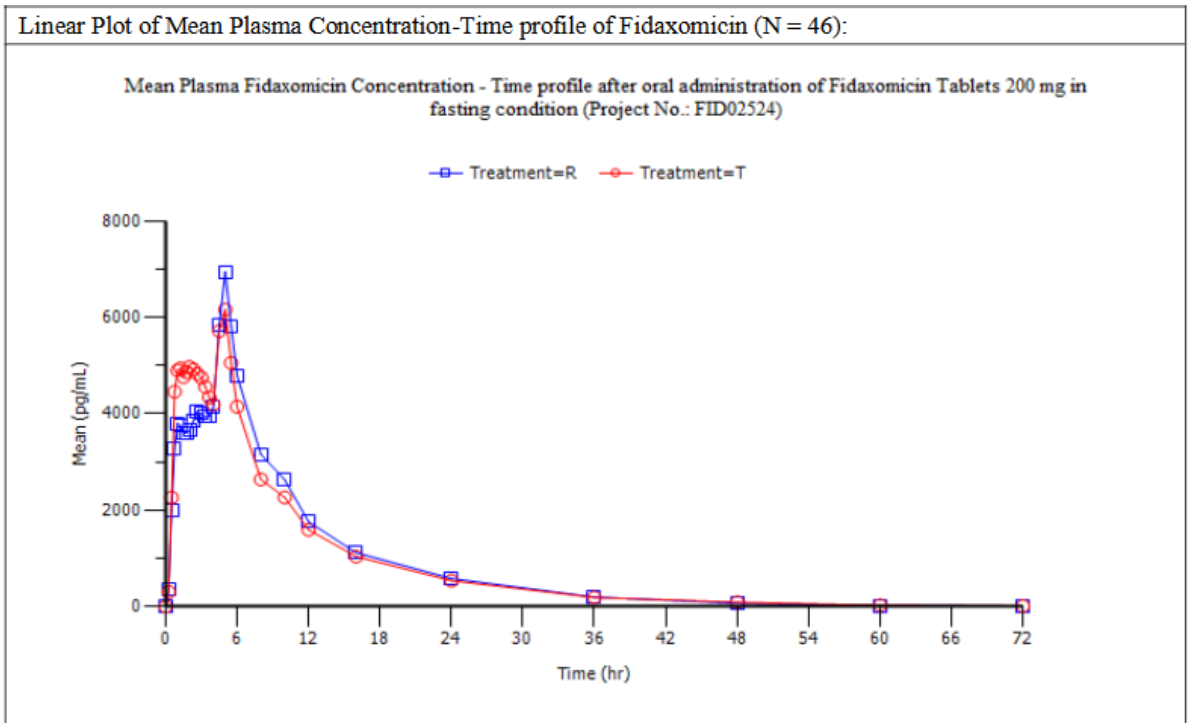

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for fidaxomicin, n=91 (46+45) (study FID02524 in the fasted state).

Treatment	**AUC_{0-t}** pg*h/ml	**C_{max}** pg//ml	**t_{max}** h
Test	**60019 ± 25030**	**9214 ± 4816**	**2.667 (0.500 - 5.500)**
Reference	**61735 ± 25255**	**8595 ± 4146**	**4.500 (0.500 - 10.000)**
***Ratio (90% CI)**	**95.74 (90.07 - 101.77)**	**104.39 (96.35 - 113.10)**	**-**

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 FID02624 in the fed state

Methods

This was a single-dose, fully replicate crossover study conducted in 50 healthy volunteers, comparing Fidaxomicin, 200 mg, tablets with Dificlir, 200 mg, tablets under fed conditions (high-fat high-calorie meal). Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of fidaxomicin 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 26th September and 19th October 2024.

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

Figure 2: Fidaxomicin mean plasma concentration – time profile (linear plot)

Linear Plot of Mean Plasma Concentration-Time profile of Fidaxomicin (N = 47):

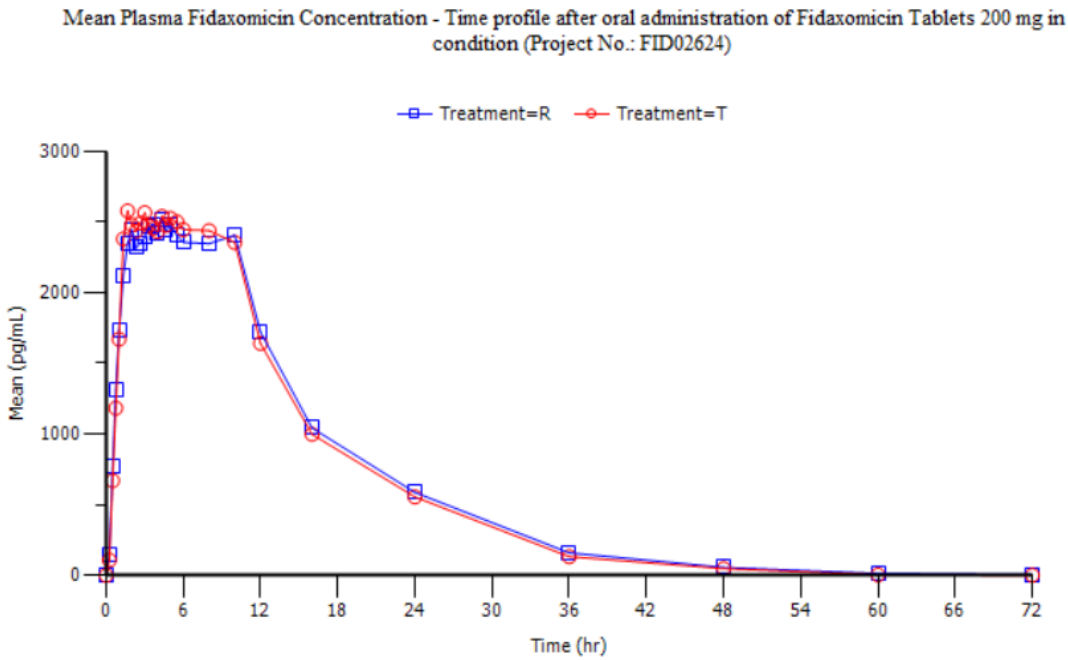

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for fidaxomicin, n=91 (47+44) (Study FID02624 in the fed state).

Treatment	AUC_{0-t} pg*h/ml	C_{max} pg//ml	t_{max} h
Test	**42149 ± 17828**	**4696 ± 2297**	**3.333 (0.500 - 12.017)**
Reference	**43173 ± 19149**	**4276 ± 1891**	**3.333 (0.500 - 10.017)**
***Ratio (90% CI)**	**97.44 (91.69 -103.56)**	**109.37 (101.58 - 117.75)**	-

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%.

Discussion and overall conclusion
Fidaxomicin SUN is an immediate-release tablet intended to have local effect in the intestine but there is some systemic absorption. According to the Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract, for

drugs with some degree of systemic bioavailability acting in the intestinal lumen or the luminal side of the membrane, bioequivalence studies based on plasma levels usually in fasting and fed state could be used as a surrogate of equivalence, if absorption is not saturated (demonstrated e.g. by means of a dose-proportionality study). According to the EPAR of the reference product, increasing the dose from 200 to 400 mg did not result in a proportional increase in fidaxomicin C_{max} or AUC_{0-t} values. There was no request to follow up on this issue as fidaxomicin is given as a fixed dose of 200 mg, but it is stated that solubility problems is likely one part of the explanation. The applicant was asked to justify that absorption is not saturated at a dose of 200 mg, in order to justify that the performed PK studies in the fasted and fed state can be used as surrogate of equivalence for this product. In response, the Applicant presented exposure data from other studies with the clinical 200 mg dose and compared it to the results with a 400 mg dose. The exposure data with the 200 mg dose from the study referred to in the EPAR regarding dose-proportionality (study OPT-80-005) appear to be higher than the exposure seen in some other studies with a 200 mg dose, eg the DDI study with cyclosporin. This might explain why almost no difference was observed between the 200 mg dose and a 400 mg dose in study OPT-80-005, considering also that the data was obtained in different subjects and that the variability in PK is large. Between-study comparisons between the 400 mg dose results from study OPT-80-005 and 200 mg dose results with other studies indicate a dose-proportional or somewhat less than dose-proportional increase. Literature data (Oshima et al) indicate no large deviations from dose-proportionality in the 100 mg-200 mg dose range. In an in vivo DDI study with cyclosporin, fidaxomicin Cmax increased 4-fold and AUC 2-fold, indicating that fidaxomicin is a P-gp substrate and that P-gp may limit absorption. Effects of P-gp on absorption would not be expected to be higher following a higher dose; rather the transporter would be expected to be saturated at a higher dose, resulting potentially in a more than dose-proportional increase in exposure with increasing doses rather than in signs of saturable absorption. Since exposure increased significantly when P-gp was inhibited, it is not considered likely that absorption as such would be saturated at this dose. Overall, although it cannot be firmly concluded that the pharmacokinetics is dose-proportional in a relevant range, considering also the results of the P-gp inhibition study, any non-linearity in PK would be expected to be due to limited solubility rather than limited absorption. Thus, it is considered sufficiently justified that absorption is not saturable at a 200 mg dose and that it would be possible to use pharmacokinetic studies in the fasted and fed state to establish therapeutic equivalence between the test and reference formulation.

The bioequivalence studies 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) and ICH M13A. Fidaxomicin has a main metabolite, OP-1118, that also shows antimicrobial activity but with a much higher MIC90 value compared to fidaxomicin (8 mg/L versus 0.25 mg/L). Although the recovery of the metabolite in faeces was about twice that of the recovery of parent drug, it is not expected that the metabolite will provide a high contribution to the efficacy of fidaxomicin. Measuring parent drug only is considered sufficient in line with the general recommendation in ICHM13A.The provided meal in the fed study is considered a high-fat high-calorie meal according to guideline recommendations. The bioanalytical methods were adequately validated. Widening of acceptance criteria was pre-specified for C_{max} in both studies. However, since results were within conventional acceptance criteria, this widening has not been assessed.

Thus, in the submitted bioequivalence studies in the fasted and fed state, the results for Fidaxomicin, 200 mg, tablets compared to Dificlir, 200 mg, tablets were within bioequivalence acceptance criteria. Therapeutic equivalence has been demonstrated between test and reference product based on pharmacokinetic data.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted.

Provided that bioequivalence with the originator product is demonstrated (see above), additional data is not necessary. Since fidaxomicin acts locally in the intestine, systemic absorption is relevant mainly for safety and as an indirect indicator of exposure in the intestinal lumen which assumes similar properties of the formulation with regard to e.g. tablet dissolution.

Pharmacovigilance system

Proposed MAH: Sun Pharmaceutical Industries (Europe) B.V., Basics GmbH, Ranbaxy (Poland) Sp. z o.o., Terapia S.A.

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 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 Fidaxomicin SUN.

Part II Safety specification

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

Part III Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which 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 0.1 signed 28 February 2025 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 Fidaxomicin SUN is found adequate. There are no objections to approval of Fidaxomicin SUN, from a non-clinical and clinical point of view. Therapeutic equivalence between the test and reference product has been adequately demonstrated based on pharmacokinetic studies. 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

Description	Due date
The Applicant has committed to submit an updated, guideline-compliant ERA within 5 years following the granting of the Marketing Authorisation. The updated ERA will include: • Updated Phase I assessment using either justification of Phase I refinement including the use of recent and representative epidemiological data, or the reference-based approach. • Updated PBT screening in case applicable. • Completeness of the ecotoxicological dataset in line with the tailored testing strategy for antibacterial medicinal products.	5 years following the granting of the Marketing Authorisation

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

- **Additional risk minimisation measures (including educational material)**
  N/A

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC**
  N/A

- **Specific obligation to complete post-authorisation measures for the marketing authorisation under Exceptional circumstances in accordance with 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 Dificlir 200 mg, film-coated tablet, EMA/857570/2011 and Morphine 1 mg/ml solution for infusion in pre-filled syringe, DE/H/6814/001-002/DC.

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
-	-	-	-	-	-