LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Lansoprazole SUN Pharma
(lansoprazole)

SE/H/2401/01-02/DC

This module reflects the scientific discussion for the approval of Lansoprazole SUN Pharma. The procedure was finalised on 2024-09-26. 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, a marketing authorisation has been granted for Lansoprazole SUN Pharma, 15 mg, 30 mg, Orodispersible tablet.

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

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Lansoprazole SUN Pharma, 15 mg, 30 mg, Orodispersible tablet, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and FR, IT and ES as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Zoton FasTab, 15 mg, Oro-Dispersible Tablets authorised in Ireland since 2001, with Pfizer Healthcare as marketing authorisation holder.

The reference product used in the bioequivalence studies (LAN07022 and LAN07122) is Zoton, 30 mg, orodispersible tablet from Italy with Pfizer Italia S.r.l. as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in CMS FR and ES: Lanzo, 15 mg, orodispersible tablet and Lanzo, 30 mg, orodispersible tablet, both authorised in Sweden since 2003, with Pfizer AB as marketing authorisation holder. The justification to use this product is based on RMS's own files. The ERP information was circulated during the validation period.

Potential similarity with orphan medicinal products
N/A

II. QUALITY ASPECTS

II.1 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.

II.2 Medicinal 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. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of lansoprazole are well known. As lansoprazole 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.

Environmental Risk Assessment (ERA)
Since Lansoprazole SUN Pharma is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Lansoprazole SUN Pharma from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted two bioequivalence studies, one in fasted state and one in fed state, comparing Lansoprazole SUN Pharma (lansoprazole), 30 mg, orodispersible tablets, with the reference product Zoton 30 mg, orodispersible tablets.

Pharmacokinetic properties of the active substance
Absorption: Enteric-coated lansoprazole has an oral bioavailability of about 80-90 %. Following a single, oral dose of lansoprazole, maximal plasma concentrations occur at approximately 1.5-2.0 hours.

Concomitant food intake decreases the bioavailability by about 50 %, and therefore lansoprazole should be administered on an empty stomach.

Linearity: The pharmacokinetics of lansoprazole is linear within the dose range 15-60 mg.

Elimination: The terminal half-life is 1-2 hours.

Study LAN07022 – 30 MG, FASTED
Methods
This was a randomised, two-treatment, four-period, two-sequence single-dose fully replicate crossover study conducted in 50 healthy volunteers, comparing Lansoprazole SUN Pharma (lansoprazole), 30 mg, orodispersible tablets, with Zoton 30 mg, orodispersible tablets, under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of lansoprazole were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-t}, C_{max} and $AUC_{0-\infty}$. The study was conducted between 2023-02-06 and 2023-05-11.

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 lansoprazole, n=48.

Pharmacokinetic parameters	Arithmetic Means (±SD)			
	Lansoprazole Gastro-Resistant Oro-Dispersible Tablets 30 mg		Zoton (lansoprazole) 30 mg Oro-Dispersible Tablets	
	Test (T1)	Test (T2)	Reference (R1)	Reference (R2)
AUC0-t (hr*ng/mL)	6456.2629 (±4938.71633)	6274.1656 (±4167.51990)	6230.1787 (±4569.15491)	6209.4175 (±4431.15174)
AUC0-inf (hr*ng/mL)	6631.4817 (±5245.39651)	6428.1300 (±4426.18479)	6395.1404 (±4866.47155)	6377.7613 (±4744.53220)
Cmax (ng/mL)	1825.826 (±614.9624)	1786.246 (±472.2170)	1755.842 (±557.0397)	1775.069 (±579.0727)
*Tmax (hr)	1.500 (0.500- 5.000)	1.625 (0.750- 3.750)	2.000 (1.000- 4.500)	1.750 (0.750- 6.000)

*Median value (Min - Max) are presented

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml
***Ratio (90% CI)**	**101.85 (97.39 - 106.51)**	**101.81 (97.39 - 106.43)**	**102.66 (96.68 - 109.02)**

AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
C_{max}	maximum plasma concentration
t_{max}	time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t}, C_{max} and $AUC_{0-\infty}$ 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 LAN07122 – 30 MG, FED

Methods

This was a randomised, two-treatment, four-period, two-sequence single-dose fully replicate crossover conducted in 50 healthy volunteers, comparing Lansoprazole SUN Pharma (lansoprazole), 30 mg, orodispersible tablets, with Zoton 30 mg, orodispersible tablets, under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of lansoprazole were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-t}, C_{max} and $AUC_{0-\infty}$. The study was conducted between 2023-02-08 and 2023-07-12.

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

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for lansoprazole, n=45.

Pharmacokinetic parameters	Arithmetic Means (±SD)			
	Lansoprazole Gastro-Resistant Oro-Dispersible Tablets 30 mg		Zoton (lansoprazole) 30 mg Oro-dispersible Tablets	
	Test (T1)	Test (T2)	Reference (R1)	Reference (R2)
AUC0-t (hr*ng/mL)	3790.1985 (±3101.38732)	3999.3485 (±3427.35355)	3383.1315 (±2583.66599)	3635.2336 (±2871.13399)
AUC0-inf (hr*ng/mL)	3991.6654 (±3320.09000)	4098.4359 (±3587.46274)	3452.5291 (±2656.28098)	3814.8670 (±3026.74889)
Cmax (ng/mL)	626.525 (±364.5416)	665.007 (±422.1756)	620.844 (±336.1112)	642.739 (±332.1986)
*Tmax (hr)	5.000 (1.500- 9.000)	4.250 (1.500- 8.000)	4.500 (1.000- 6.500)	4.250 (1.500- 9.000)

*Median value (Min - Max) are presented

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml
***Ratio (90% CI)**	**109.68 (104.16 - 115.49)**	**109.70 (104.83 – 114.79)**	**100.22 (92.75 – 108.29)**

AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
C_{max}	maximum plasma concentration
t_{max}	time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t}, C_{max} and $AUC_{0-\infty}$ 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 15 mg.

Discussion and overall conclusion
The application concerns a gastro-resistant orodispersible tablet formulation and according to Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CHMP/EWP/280/96 Rev1), in gastro-resistant or enteric products bioequivalence should be demonstrated not only in a single dose study in fasted conditions, but also in a single dose study under fed conditions. The bioequivalence studies and its statistical evaluation were also 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.

Absence of studies with the additional strength of 15 mg is acceptable, as all conditions for biowaiver for additional strength, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of lansoprazole is linear between 15 mg and 60 mg. Furthermore, according to Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CHMP/EWP/280/96 Rev1), for multiple unit formulations of a medicinal product with several strengths, it is sufficient to conduct the studies only at the highest/most sensitive strength if the compositions of the strengths are proportional, the formulations contain identical beads or pellets (and these are produced by the same manufacturing process) and the dissolution profiles are similar. The highest strength has been studied which is in accordance with guideline recommendations. Thus, absence of studies with the additional strength is acceptable from a pharmacokinetic point of view.

Based on the submitted bioequivalence studies, Lansoprazole SUN Pharma (lansoprazole) 30 mg, orodispersible tablets is considered bioequivalent with Zoton, 30 mg, orodispersible tablets.

The results of studies LAN07022 and LAN07122 with 30 mg formulation CAN be extrapolated to the other strength 15 mg, according to conditions in the Guideline on the investigation of Bioequivalence; CHMP/QWP/EWP/1401/98 Rev. 1, section 4.1.6.

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, additional data is not necessary.

Risk Management Plan
The MAH has submitted an *updated* 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 Lansoprazole SUN Pharma.

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**

The proposed updated summary of safety concerns is acceptable.

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.

The safety information is aligned to the reference medicinal product Zoton FasTab 15 orodispersible tablets, Zoton FasTab 30 mg oro-dispersible tablets approved in IE.

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. The submitted Risk Management Plan, version 0.2 signed 14-Dec-2023 is 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.

V. USER CONSULTATION

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. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Lansoprazole SUN Pharma, is found adequate. There are no objections to approval of Lansoprazole SUN Pharma, 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.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment
N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC
N/A

VII. APPROVAL

The decentralised procedure for Lansoprazole SUN Pharma, 15 mg, 30 mg, Orodispersible tablet was positively finalised on 2024-09-26.

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Public Assessment Report – Update

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

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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