LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Nexizol
(esomeprazole magnesium)

SE/H/2302/01/DC

This module reflects the scientific discussion for the approval of Nexizol. The procedure was finalised on 2023-06-21. 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, a marketing authorisation has been granted for Nexizol, 10 mg, gastro-resistant granules for oral suspension in sachet.

The active substance is esomeprazole magnesium. 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 Nexizol, 10 mg, gastro-resistant granules for oral suspension in sachet, 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 DK and NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Nexium, 10 mg, gastro-resistant granules for oral suspension in sachet authorised in Sweden since 2007, with Grünenthal GmbH as marketing authorisation holder.

The reference product used in the bioequivalence studies is Nexium, 10 mg, gastro-resistant granules for oral suspension in sachet from Germany with Grünenthal GmbH as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

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 esomeprazole are well known. As esomeprazole 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)
Since Nexizol 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 Nexizol from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted two bioequivalence studies comparing Nexizol (Esomeprazole, 10 mg, gastro-resistant granules) with the reference product Nexium.

Pharmacokinetic properties of the active substance
Absorption: Esomeprazole is acid labile and is administered orally as enteric-coated granules. *In vivo* conversion to the R-isomer is negligible. Absorption of esomeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Elimination: The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing.

Study 615-18 - Fasting
Methods
This was a randomised, two-treatment, two-period, two-sequence single-dose crossover study conducted in 56 healthy volunteers, comparing Esomeprazole, 10 mg, gastro-resistant granules for oral suspension with Nexium, 10 mg, gastro-resistant granules for oral suspension under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 20 hours post-dose. Plasma concentrations of esomeprazole were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. The study was conducted between 2018-12-27 and 2019-01-05.

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

Table 1. Pharmacokinetic parameters, uncorrected (non-transformed values; arithmetic mean ± SD,
t_{max} median, range) for esomeprazole, n=55.

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1259.27 ± 806.23**	**1268.76 ± 813.48**	**434.42 ± 175.75**	**2.25 (1.25-4.00)**
Reference	**1187.71 ± 723.79**	**1211.73 ± 725.40^**	**393.58 ± 152.85**	**2.00 (0.75-4.00)**
***Ratio (90% CI)**	**106.76 (100.38-113.56)**	**105.68 (99.56-112.18)**	**110.21 (102.10-118.96)**	**-**

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*
^indicates n=54. As the subject no. 37 was not exhibit a log linear relationship in the terminal elimination phase in the concentration versus time profile in the treatment of reference (R).

For AUC_{0-t}, $AUC_{0-\infty}$ 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 616-18 - Fed
Methods
This was a randomised, two-treatment, four-period, two-sequence, full-replicate single-dose crossover study conducted in 50 healthy volunteers, comparing Esomeprazole, 10 mg, gastro-resistant granules for oral suspension with Nexium, 10 mg, gastro-resistant granules for oral suspension under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of esomeprazole were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. The study was conducted between 2018-12-26 and 2019-02-02.

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

Table 2. Pharmacokinetic parameters, uncorrected (non-transformed values; arithmetic mean ± SD,
t_{max} median, range) for esomeprazole, n=94.

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$^ ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1001.48 ± 679.77**	**1021.24 ± 685.23**	**231.33 ± 108.67**	**4.50 (1.00-6.50)**
Reference	**1070.69 ± 721.11**	**1085.74 ± 735.26**	**234.53 ± 110.74**	**4.50 (1.00-8.00)**
***Ratio (90% CI)**	**92.77 (88.03-97.75)**	**92.66 (87.98-97.58)**	**98.33 (91.69-105.46)**	**-**

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*

^Indicates n=93, Subject no. 05 for test (T1) and subject no. 40 for reference (R1) did not exhibit log linear relationship in the terminal elimination phase as R^2 value was found to be less than 0.8, i.e. 0.7985 and 0.6535.

For AUC_{0-t}, $AUC_{0-\infty}$ 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 studies and the 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 Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CHMP/EWP/280/96). The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence studies, Nexizol is considered bioequivalent with Nexium.

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 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 Nexizol.

Safety specification
The MAH has submitted the version 0.1 RMP dated 11 July, 2022 and proposed the following summary safety concerns:

Table Part SVIII.1: Summary of safety concerns

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

The proposed safety concerns for Nexizol is completely in line with that of the reference product.

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

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

Summary of the RMP
The submitted Risk Management Plan, version 0.1 RMP signed 11 July, 2022 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.

V. USER CONSULTATION

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 Nexium 10 mg gastro-resistant granules for oral suspension, sachet SE/H/234/04/MR and Dexamcol 1 mg/ml + 5 mg/ml eye drops, solution DK/H/3155/001/DC.

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Nexizol, is found adequate. There are no objections to approval of Nexizol, 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 Nexizol, 10 mg, gastro-resistant granules for oral suspension in sachet was positively finalised on 2023-06-21.

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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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