LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Striroxin
(levothyroxine sodium, anhydrous)

SE/H/2493/01-08/DC

This module reflects the scientific discussion for the approval of Striroxin. The procedure was finalised on 2024-09-25. 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 Striroxin, 25 microgram, 50 microgram, 75 mikrogram, 100 microgram, 125 microgram, 150 microgram, 175 microgram, 200 microgram, Tablet.

The active substance is levothyroxine sodium, anhydrous. 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 Striroxin, 25 microgram, 50 microgram, 75 microgram, 100 microgram, 125 microgram, 150 microgram, 175 microgram, 200 microgram, 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 DK and FI as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Euthyrox, 25 microgram, Tablet authorised in SE since 2000, with Merck Healthcare Germany GmbH as marketing authorisation holder.

The reference product used in the bioequivalence study is Euthyrox, 200 microgram, Tablet from DE with Merck BV Tupolevlaan 41-61 119 NW Schiphol-Rijk as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in CMS FI: Euthyrox, 25 microgram, 50 microgram, 75 microgram, 100 microgram, 125 microgram, 150 microgram, 175 microgram, 200 microgram, Tablet, authorised in SE since 2001, with Merck AB and Merck Germany 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 levothyroxine are well known. As levothyroxine 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 Striroxin 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 Striroxin from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has submitted one bioequivalence study in the fasted state with the highest strenght in a dose of 600 µg (3 x 200 µg) comparing Striroxin with the reference product Euthyrox.
According to the product-specific bioequivalence guidance for Levothyroxine tablets 12.5 mcg, 25 mcg, 50 mcg, 75 mcg, 100 mcg and 200 mcg (and additional strengths within the range) (EMA/CHMP/176098/2020), a single-dose, cross-over study in the fasting state with a single supra-therapeutic dose of 600 mcg of test and reference product should be administered and the 90% confidence interval should be within 90.00-111.11% for AUC_{0-72h} and within 80.00-125.00% for C_{max}.

Study C1B01495
Methods
This was a single-dose, two-way crossover study conducted in 34 healthy volunteers, comparing 3 tablets of Striroxin, 200 µg with 3 tablets of Euthyrox, 200 µg under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Serum concentrations of levothyroxine were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-72h} and C_{max} (baseline corrected for levothyroxine). The study was conducted between December 2021 and March 2022.

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 baseline corrected data of levothyroxine, n=33.

Treatment	AUC_{0-72h} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	3318.0 ± 568.9	92.28 ± 16.58	2.50 (1.50 - 4.57)
Reference	3127.7 ± 651.8	82.57 ± 14.78	3.50 (1.50 - 6.00)
***Ratio (90% CI)**	107.13 (103.34-111.07%)	111.93 (107.69-116.35%)	-
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_{0-72h} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the acceptance ranges of 90.00-111.11% and 80.00-125.00%, respectively.

A biowaiver was sought for the additional strengths of 25, 50, 75, 100, 125, 150 and 175 µg.

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) and the product-specific bioequivalence guidance for Levothyroxine tablets (EMA/CHMP/176098/2020). The bioanalytical methods were adequately validated.

Absence of studies with the additional strengths of 25, 50, 75, 100, 125, 150 and 175 µg are acceptable from a pharmacokinetic view.

Based on the submitted bioequivalence study, Striroxin is considered bioequivalent with Euthyrox.

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 Striroxin.

Part II Safety specification

Important Identified Risks	• None
Important Potential Risks	• Circulatory collapse in very low birth weight preterm neonates
Missing Information	• None

Assessor's comment: In the Summary of Safety Concerns for the reference product "Circulatory collapse in very low birth (preterm) neonate" is stated under "Important potential risks" (RMP v. 6.0). This statement was missing, and the MAH was requested to amend this. An updated RMP was submitted D106.

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 MAH has satisfactorily responded to the questions raised and updated the RMP accordingly.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.2 signed date 2024-04-10 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

The user test was assessed and accepted at day 120.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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

Post approval commitments
The applicant commits to replace the azo-based colouring agents currently included in some of the strengths by less problematic, iron-oxide based alternatives. As time is limited during the procedure, the applicant proposes to introduce these changes post-approval but prior to commercialisation of the drug product. Further commitments are made with respect to manufacturing process validation and amending the stability testing programme.

The applicant shall according to the commitment letter complete the necessary composition and manufacturing process changes within one (1) year.

The changes will be introduced through a variation procedure according to the Commission Regulation.

The strategy is accepted.

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

N/A

VII. APPROVAL

The decentralised procedure for Striroxin, 25 microgram, 50 microgram, 75 microgram, 100 microgram, 125 microgram, 150 microgram, 175 microgram, 200 microgram, Tablet was positively finalised on 2024-09-25.

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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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