LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Sapropterin Aurobindo
(sapropterin dihydrochloride)

SE/H/2221/01/DC

This module reflects the scientific discussion for the approval of Sapropterin Aurobindo. The procedure was finalised on 2023-01-18. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Sapropterin Aurobindo, 100 mg, Soluble tablet.

The active substance is sapropterin dihydrochloride, sapropterin. 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 Sapropterin Aurobindo, 100 mg, soluble 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 DE, ES, FR, IT, NL and PT as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Kuvan, 100 mg, soluble tablet authorised in the Union since 2008, with BioMarin International Limited as marketing authorisation holder.

The reference product used in the bioequivalence study is Kuvan, 100 mg, soluble tablet from Netherlands with BioMarin International Limited 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 the following medicinal product(s) has/have been designated as orphan medicinal products, but not yet been granted a marketing authorisation in the EU: EU/3/16/1784; EU/3/03/163 and EU/3/21/2435.

The applicant should monitor these products during the entire procedure to check if a marketing authorisation has been granted. In case a marketing authorisation is granted, the applicant should update the report on similarity (Module 1.7.1) and, if applicable, submit the data to support derogation from orphan market exclusivity (Module 1.7.2).

The applicant has provided a similarity report (Module 1.7.1) due to potential similarity with authorised orphan medicinal product(s) under market exclusivity. The detailed RMS assessment of similarity was presented in the RMS Similarity AR circulated at day 70.

Conclusion

Having considered the arguments presented by the applicant and with reference to Article 8 of Regulation (EC) No 141/2000, Sapropterin Aurobindo is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Palynziq.

Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Palynziq in the treatment of *patients with phenylketonuria (PKU) aged 16 years and older who have inadequate blood phenylalanine control (blood phenylalanine levels greater than 600 micromol/l) despite prior management with available treatment options*, does not prevent the granting of the marketing authorisation of Sapropterin Aurobindo. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation 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 sapropterin are well known. As sapropterin 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 Sapropterin Aurobindo is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one single-dose bioequivalence study comparing Sapropterin Aurobindo with the reference product Kuvan.

Pharmacokinetic properties of the active substance
Absorption: Sapropterin is absorbed after oral administration of the dissolved tablet, and the maximum blood concentration (C_{max}) is achieved 3 to 4 hours after dosing in the fasted state. The rate and extent of absorption of sapropterin is influenced by food. The absorption of sapropterin is higher after a high-fat, high-calorie meal as compared to fasting, resulting, in average, in 40-85% higher maximum blood concentrations achieved 4 to 5 hours after administration. The tablets should be administered with a meal to increase the absorption.

Absolute bioavailability or bioavailability for humans after oral administration is not known.

Elimination: The mean terminal half-life was 6.69 hours (range 3.91 to 16.6 hours).

Study 330-19

Methods

This was a single-dose, two-way crossover study conducted in 54 healthy volunteers, comparing Sapropterin dihydrochloride, 100 mg, soluble tablet with Kuvan, 100 mg, soluble tablet at a dose of 10 mg/kg under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 36 hours post-dose. Baseline levels of sapropterin was measured in plasma at -1.00, -0.50 and 0.00 hours before dosing. The mean of the pre-dose levels was used for the baseline adjustment of the post-dose levels. Plasma concentrations of sapropterin were determined with a 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 14/09/21 and 25/09/21.

Results

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

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for sapropterin (baseline corrected), n=53.

Treatment	**AUC_{0-t}** **ng*h/ml**	**C_{max}** **ng/ml**	**t_{max}** **h**
Test	**557.17 ± 139.59**	**87.32 ± 22.58**	**4.50 (2.50-5.50)**
Reference	**558.57 ± 147.08**	**87.12 ± 21.17**	**4.50 (3.00-5.50)**
***Ratio (90% CI)**	**99.48 (95.55-103.58)**	**99.46 (95.53-103.56)**	**-**
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*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for sapropterin (baseline uncorrected), n=53.

Treatment	**AUC_{0-t}** **ng*h/ml**	**C_{max}** **ng/ml**	**t_{max}** **h**
Test	**626.11 ± 153.08**	**89.28 ± 22.93**	**4.50 (2.50-5.50)**
Reference	**630.56 ± 151.92**	**89.14 ± 21.39**	**4.50 (3.00-5.50)**
***Ratio (90% CI)**	**98.86 (95.18-102.68)**	**99.41 (95.49-103.48)**	**-**
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 baseline corrected 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). Baseline corrected sapropterin data was used for the bioequivalence assessment, which is adequate. The bioanalytical method was adequately validated.

Based on the submitted bioequivalence study, Sapropterin Aurobindo is considered bioequivalent with Kuvan.

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 Sapropterin Aurobindo.

Safety specification

The MAH has submitted the revised RMP version 1.1 dated 29 November 2022 where the RMP has been changed from <invented name> to the approved product name "Sapropterin Aurobindo". The following table of proposed safety concerns are the same as for the previous RMP version 1.0:

Summary of safety concerns	
Important identified risks	Hypersensitivity
	Hypophenylalaninaemia
	Interaction with vasodilators using NO metabolism, Dihydrofolate reductase inhibitor (DHFR inhibitor), or levodopa
Important potential risks	Behavioral change
	Convulsion, including worsening
	Epigastric ulcer
	Gastroesophageal reflux disease
	Nephrotoxicity
	Nephrolithiasis
	New-onset anxiety disorder
	Worsening psychiatric disorder
Missing information	Size of safety database
	Long-term use
	Limited BH4 deficiency data
	Subgroup experience: • Use in the elderly • Use in breast-feeding • Use in patients with hepatic failure • Use in patients with renal failure • Use in patients with moderate to severe neurocognitive disability

The proposed safety concern is in line with the latest approved RMP version of the reference product Kuvan.

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 1.1 signed 29 November 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 Kuvan 100 mg soluble tablets, EMEA/H/C/000943 and Metoprolol Aurobindo 50 mg & 100 mg film-coated tablets, SE/H/1201/001-002/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 Sapropterin Aurobindo is found adequate. There are no objections to approval of Sapropterin Aurobindo 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 ratio is considered positive, and the application for Sapropterin Aurobindo, 100 mg, Soluble tablet 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 Sapropterin Aurobindo, 100 mg, Soluble tablet was positively finalised on 2023-01-18.

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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)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se