COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Sapropterine Teva 100 mg, soluble tablets

(sapropterin dihydrochloride)

NL/H/5309/001/DC

Date: 19 May 2022

This module reflects the scientific discussion for the approval of Sapropterine Teva 100 mg, soluble tablets. The procedure was finalised at 2 March 2022. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Sapropterine Teva 100 mg, soluble tablets, from Teva B.V.

The product is indicated for the treatment of hyperphenylalaninaemia (HPA) in adults and paediatric patients of all ages with phenylketonuria (PKU) who have been shown to be responsive to such treatment (see SmPC section 4.2).

The product is also indicated for the treatment of hyperphenylalaninaemia (HPA) in adults and paediatric patients of all ages with tetrahydrobiopterin (BH4) deficiency who have been shown to be responsive to such treatment (see SmPC section 4.2).

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Kuvan 100 mg, soluble tablets which has been registered in the EEA by BioMarin International Limited since 2 December 2008.

The concerned member states (CMS) involved in this procedure were Bulgaria, France, Germany, Norway, Portugal, Spain and Sweden.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

Potential similarity with orphan medicinal products

The MAH has provided a similarity report due to potential similarity with the authorised orphan medicinal product under market exclusivity:

Tradename (act. subst.):	**Orphan design. nr:**	**Date:**	**Expiry orphan status:**
Palynziq (pegvaliase)	EU/3/09/708	08/05/2019	08/05/2029

Having considered the arguments presented by the MAH and with reference to Article 8 of Regulation (EC) No 141/2000, Sapropterine Teva 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 hyperphenylalaninaemia, does not prevent the granting of the marketing authorisation of Sapropterine Teva. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

II. QUALITY ASPECTS

II.1 Introduction

Sapropterine Teva is a off-white to light yellow, round soluble tablet with "L71" imprinted on one side and "T" on the other side. Each tablet contains 100 mg of sapropterin dihydrochloride (equivalent to 77 mg of sapropterin).

The soluble tablets are packed in high-density polyethylene (HDPE) bottles with child-resistant closure. The bottles are sealed with an aluminium seal and contain a small plastic tube of desiccant (silica gel).

The excipients are: mannitol (E421), pregelatinised starch, crospovidone (E1202), riboflavin (E101), ascorbic acid (E300) and sodium stearyl fumarate

II.2 Drug Substance

The active substance is sapropterin dihydrochloride, an established active substance however not described in the European Pharmacopoeia (Ph.Eur.) or any other pharmacopeia. The active substance is an off-white to pale yellow crystalline powder and is freely soluble in water. Sapropterin dihydrochloride has three chiral centres and is manufactured as Form B (dichloride salt in anhydrate form).

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process is divided in two parts. The first part manufactures an intermediate and the second part manufactures the active substance within four stages. No class I solvents are used during the synthesis. The active substance has been adequately characterised and acceptable specifications have been adopted for the solvents and reagents. The starting material and its specifications are acceptable.

Quality control of drug substance

The active substance specification has been established in house and is considered adequate to control the quality. The active substance specification includes tests and limits for description, identification, solubility, loss on drying, water content, sulphated ash, specific optical rotation, chloride content, platinum content, related substances, assay, microbial

contamination and residual solvents. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three production scaled batches.

Stability of drug substance

Stability data on the active substance have been provided for three production scaled batches stored at 25°C/60% RH (6 months) and 5°C (9 months). No clear up- or downward trends are observed during the accelerated and long term stability studies. The claimed retest period of 18 months for the drug substance when stored at 2-8°C is acceptable.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. Formulation development focused on evaluation of high risk formulation variables identified in an initial risk assessment. The initial tablet was designed to be similar to the reference product. For the studies, the amount of excipients in the formulation was varied whilst keeping the core tablet weight constant. The weight was adjusted by using the mannitol granules. A bioequivalence study has been performed under fed conditions comparing the test product and the reference product Kuvan. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The tablets are prepared by wat granulation. The particle size of the components is controlled by sieving/screening and milling when required. Then, the final blend is compressed into tablets. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for two pilot scaled batches and one smaller batch in accordance with the relevant European guidelines. The provided process validation scheme is acceptable. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post authorisation.

Control of excipients

The excipients comply with Ph. Eur. requirements. The specifications are acceptable and functionality related characteristics have been discussed in sufficient detail.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identity, water content, dissolution, assay, uniformity of dosage units, ascorbic acid content, disintegration time, resistance to crushing, related substances and microbial contamination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from two pilot scaled batches and one smaller batch from the

proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for one pilot scaled and two minimum production scaled batches stored at 25°C/60% RH (12 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. All parameters stay within the proposed acceptance limits during all conditions. Photostability studies were performed in accordance with ICH recommendations and showed that the product is not stable when exposed to light since the tablets turned from light yellow to dark yellow upon direct exposure to light. On basis of the data submitted, a shelf life was granted of 2 years. The labelled storage conditions are: "This medicinal product does not require any special temperature storage conditions. Store in the original package to protect from moisture and light."

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Sapropterine Teva has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Sapropterine Teva is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Kuvan which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is

no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Sapropterin dihydrochloride is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Sapropterine Teva 100 mg, soluble tablets (Teva B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Kuvan 100 mg soluble tablets (BioMarin International Limited, Ireland).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and composition of the EU reference product. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 42 healthy male and female subjects, aged 18-45 years. Each subject received a single oral dose (7 x 100 mg) of one of the 2 sapropterin formulations. The dissolved tablets were orally administered with a total of 240 ml water 30 minutes after a high calorie, high fat breakfast (consisting of bread, egg omelette, fried chicken, French fries and milk). There were dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.500, 1.000, 1.500, 2.000, 2.333, 2.667, 3.000, 3.333, 3.667, 4.000, 4.333, 4.667, 5.000, 5.333, 5.667, 6.000, 6.500, 7.000, 8.000, 12.000, 16.000, 24.000 and 48.000 hours after administration of the products.

The design of the study is acceptable. A study conducted under fed conditions is appropriate as the rate and extent of absorption of sapropterin is influenced by food.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Two subjects withdrew from the study due to adverse events, one subject was withdrawn due to a positive alcohol test and one subjects did not report to the facility for the second period. Therefore, 38 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sapropterin (tetrahydrobiopterin, BH4 under fed conditions.

Treatment N=38	**AUC_{0-t} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	334.71	57.79	4.00 (2.33 – 6.50)
Reference	323.45	58.48	3.83 (2.33 – 5.70)
***Ratio (90% CI)**	1.03 (0.97 – 1.11)	0.99 (0.92 – 1.06)	--
CV (%)	17.41	18.48	--

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 concentration
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Sapropterine Teva is considered bioequivalent with Kuvan.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 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 Sapropterine Teva.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Hypersensitivity • Hypophenylalaninaemia • Interaction with vasodilators using NO metabolism, DHFR Inhibitors, or levodopa
Important potential risks	• Behavioural change • Convulsion, including worsening • Epigastric ulcer • Gastroesophageal reflux disease • Nephrotoxicity • Nephrolithiasis • New-onset anxiety disorder • Worsening psychiatric disorder
Missing information	• 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 member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Kuvan. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 test consisted of: a pilot test, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

Sapropterine Teva 100 mg, soluble tablets has a proven chemical-pharmaceutical quality and is a generic form of Kuvan 100 mg, soluble tablets. Kuvan is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Sapropterine Teva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 2 March 2022.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse