Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Sapropterin dihydrochloride 100 mg Soluble Tablets

(sapropterin dihydrochloride)

PL 00289/2530

Teva UK Limited

LAY SUMMARY

Sapropterin dihydrochloride 100 mg Soluble Tablets (sapropterin dihydrochloride)

This is a summary of the Public Assessment Report (PAR) for Sapropterin dihydrochloride 100 mg Soluble Tablets. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Sapropterin dihydrochloride Soluble Tablets in this lay summary for ease of reading.

For practical information about using Sapropterin dihydrochloride Soluble Tablets , patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Sapropterin dihydrochloride Soluble Tablets and what are they used for?
This application is for a generic medicine. This means that this is the same as, and considered interchangeable with, a reference medicine already authorised in the United Kingdom (UK) and the European Union (EU) called Kuvan 100 mg soluble tablets.

Sapropterin dihydrochloride Soluble Tablets are used to treat hyperphenylalaninaemia (HPA) or phenylketonuria (PKU) in patients of all ages. HPA and PKU are due to abnormally high levels of phenylalanine in the blood which can be harmful. Sapropterin dihydrochloride Soluble Tablets reduces these levels in some patients who respond to tetrahydrobiopterin (BH4) and can help increase the amount of phenylalanine that can be included in the diet.

This medicine is also used to treat an inherited disease called BH4 deficiency in patients of all ages, in which the body cannot produce enough BH4. Because of very low BH4 levels phenylalanine is not used properly and its levels rise, resulting in harmful effects.

How do Sapropterin dihydrochloride Soluble Tablets work?
Sapropterin dihydrochloride Soluble Tablets contain the active substance ,sapropterin (as sapropterin dihydrochloride), which is a synthetic copy of the body's own substance called tetrahydrobiopterin (BH4). BH4 is required by the body to use an amino acid called phenylalanine, in order to build another amino acid called tyrosine. By replacing the BH4 that the body cannot produce, Sapropterin dihydrochloride Soluble Tablets reduce the harmful excess of phenylalanine in the blood and increase the dietary tolerance to phenylalanine

How are Sapropterin dihydrochloride Soluble Tablets used?
The pharmaceutical form of this medicine is soluble tablet and the route of administration is oral (taken by mouth).

Dosing for PKU
The recommended starting dose of Sapropterin dihydrochloride Soluble Tablets in patients with PKU is 10 mg for each kg of body weight. The patient should take Sapropterin dihydrochloride Soluble Tablets as a single daily dose with a meal to increase the absorption, and at the same time each day, preferably in the morning. The doctor may adjust their patient's dose, usually between 5 and 20 mg for each kg of body weight per day, depending on their patient's condition.

Dosing for BH4 deficiency
The recommended starting dose of Sapropterin dihydrochloride Soluble Tablets in patients with BH4 deficiency is 2 to 5 mg for each kg of body weight. The patient should take Sapropterin dihydrochloride Soluble Tablets with a meal to increase the absorption. Divide the total daily dose into 2 or 3 doses, taken over the day.

The patient's doctor may adjust their patient's dose up to 20 mg for each kg of body weight per day, depending on their patient's condition.

The table below is an example of how an appropriate dose is calculated.

Body weight (kg)	Number of 100 mg tablets (dose 10 mg/kg)	Number of 100 mg tablets (dose 20 mg/kg)
10	1	2
20	2	4
30	3	6
40	4	8
50	5	10

Method of administration
For PKU patients, the total daily dose is taken once a day at the same time each day, preferably in the morning.

For BH4 deficiency patients, the total daily dose is divided into 2 or 3 doses over the day.

Use in all patients
The patient/caregiver should place the prescribed number of tablets in a glass or cup of water, as accurately described below, and stir until dissolved.

It may take a few minutes for the tablets to dissolve. To make the tablets dissolve faster the patient/caregiver can crush them. Small particles may be visible in the solution, but they will not affect the effectiveness of the medicine. The patient should drink the dissolved preparation of Sapropterin dihydrochloride Soluble Tablets with a meal within 15 to 20 minutes of its preparation.

The patient should not swallow the desiccant capsule contained in the bottle.

Use in patients above 20 kg body weight
The patient/caregiver should place the tablets in a glass or cup (120 to 240 ml) of water and stir until dissolved.

Use in children up to 20 kg body weight
The dose is based on body weight. This will change as the child grows. The child's doctor will tell the caregiver:
- the number of Sapropterin dihydrochloride Soluble Tablets needed for one dose
- the amount of water needed to mix one dose of Sapropterin dihydrochloride Soluble Tablets
- the amount of solution the caregiver will need to give their child for their prescribed dose.

The child should drink the solution with a meal.

The caregiver, should give their child the prescribed amount of solution within 15 to 20 minutes after dissolving. If the caregiver is not able to give their child's dose within 15 to 20 minutes after dissolving the tablets, they will need to prepare a new solution as the unused solution should not be used beyond 20 minutes.

Supplies needed to prepare and give the child's dose of Sapropterin dihydrochloride Soluble Tablets

- the number of Sapropterin dihydrochloride Soluble Tablets needed for one dose
- a medicine cup with graduation markings at 20, 40, 60 and 80 ml
- a glass or cup
- a small spoon or clean utensil for stirring
- an oral syringe (graduated in 1 ml divisions) (10 ml syringe for administration of volumes of 10 ml or 20 ml syringe for administration of volumes of >10 ml).

The patient or caregiver should ask their doctor for the medicine cup for dissolving the tablets and the 10 ml or 20 ml oral syringe, if they do not have these supplies.

Steps for preparing and taking the dose:

- The caregiver should place the prescribed number of tablets in the medicine cup. They should then pour the amount of water into the medicine cup, as instructed by the patient's doctor (e.g. the doctor told the caregiver to use 20 ml for dissolving one Sapropterin dihydrochloride Soluble Tablet). The caregiver should check to make sure that the amount of liquid lines up with the amount that the doctor has told them and stir with the small spoon or clean utensil until the tablets dissolve.
- If the patient's doctor has told the caregiver to administer only a portion of the solution, the caregiver should point the tip of the oral syringe into the medicine cup. Then slowly pull back the plunger to withdraw the amount as instructed by the doctor.
- The caregiver should transfer the solution by pushing on the plunger slowly until all of the solution in the oral syringe is transferred to a glass or cup for administration (e.g. if the patient's doctor told the caregiver to dissolve two Sapropterin dihydrochloride Soluble Tablets in 40 ml water and administer 30 ml to the child, the caregiver would have to use the 20 ml oral syringe two times to draw up 30 ml (e.g. 20 ml + 10 ml) of the solution and transfer it to a glass or cup for administration). Use a 10 ml oral syringe for administration of volumes 10 ml or a 20 ml oral syringe for administration of volumes >10 ml.
- If the baby is too small to drink from a glass or a cup the caregiver may administer the solution via the oral syringe. The caregiver should draw up the prescribed volume from the solution prepared in the medicine cup and place the tip of the oral syringe into the baby's mouth. Then point the tip of the oral syringe towards either cheek. The caregiver should then push on the plunger slowly, a small amount at a time, until all of the solution in the oral syringe is given.
- The caregiver should throw away any remaining solution and follow the following instructions: Remove the plunger from the barrel of the oral syringe. Wash both parts of the oral syringe and the medicine cup with warm water and air dry. When the oral syringe is dry, put the plunger back into the barrel. Store the oral syringe and the medicine cup for next use.

For further information on how Sapropterin dihydrochloride Soluble Tablets are used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Sapropterin dihydrochloride Soluble Tablets have been shown in studies?
As Sapropterin dihydrochloride Soluble Tablets are a generic medicine, studies in healthy volunteers have been limited to tests to determine that this medicine is bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Sapropterin dihydrochloride Soluble Tablets?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

As Sapropterin dihydrochloride Soluble Tablets are a generic medicine and are bioequivalent to the reference medicine, the possible side effects are considered to be the same as the reference medicine.

Why were Sapropterin dihydrochloride Soluble Tablets approved?
It was concluded that, Sapropterin dihydrochloride Soluble Tablets have been shown to be of comparable quality and to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Sapropterin dihydrochloride Soluble Tablets?
A Risk Management Plan (RMP) has been developed to ensure that Sapropterin dihydrochloride Soluble Tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Sapropterin dihydrochloride Soluble Tablets
A Marketing Authorisation was granted in the UK on 01 October 2021.

The full PAR for Sapropterin dihydrochloride Soluble Tablets follows this summary.

This summary was last updated in November 2021.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Sapropterin dihydrochloride 100 mg Soluble Tablets (PL 00289/2530) could be approved.

The product is approved for the following indications:

- Sapropterin dihydrochloride 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.

- Sapropterin dihydrochloride is also indicated for the treatment of HPA in adults and paediatric patients of all ages with tetrahydrobiopterin (BH4) deficiency who have been shown to be responsive to such treatment.

The active substance, sapropterin dihydrochloride, is a synthetic version of the naturally occurring 6R-BH4, which is a cofactor of the hydroxylases for phenylalanine, tyrosine and tryptophan. The rationale for administration of Sapropterin dihydrochloride in patients with BH4-responsive PKU is to enhance the activity of the defective phenylalanine hydroxylase and thereby increase or restore the oxidative metabolism of phenylalanine sufficient to reduce or maintain blood phenylalanine levels, prevent or decrease further phenylalanine accumulation, and increase tolerance to phenylalanine intake in the diet. The rationale for administration of Sapropterin dihydrochloride in patients with BH4 Deficiency is to replace the deficient levels of BH4, thereby restoring the activity of phenylalanine hydroxylase.

This application was approved under Regulation 51B of The Human Medicines Regulations 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicine of a suitable originator medicinal product, Kuvan 100 mg soluble tablets, that has been licensed within the United Kingdom (UK) and the European Union (EU) for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product. The bioequivalence study was conducted in line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A national Marketing Authorisation was granted in the UK on 01 October 2021.

II QUALITY ASPECTS

II.1 Introduction

This product contains 100 mg of sapropterin dihydrochloride (equivalent to 77 mg of sapropterin) in each soluble tablet.

In addition to sapropterin dihydrochloride, this product also contains the excipients mannitol (E421), pregelatinised starch, crospovidone (E1202), riboflavin (E101), ascorbic acid (E300) and sodium stearyl fumarate.

The finished product is packaged in high-density polyethylene (HDPE) bottles, each with either a white or green child-resistant closure. Each bottle contains 30 or 120 tablets. The bottles are sealed with an aluminium seal. Each bottle contains a small plastic tube of desiccant (silica gel). Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

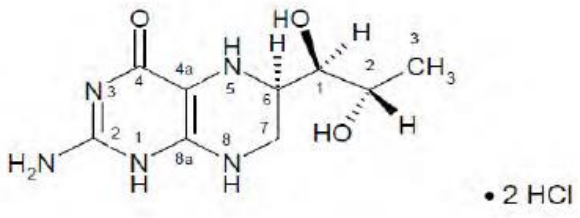
II.2 ACTIVE SUBSTANCE

rINN: Sapropterin dihydrochloride

Chemical Name: 6R)-2-amino-6-[(1R,2S)-1,2-dihydroxypropyl]-5,6,7,8-tetrahydro-4(1H)-pteridinone dihydrochloride

Molecular Formula: $C_9H_{15}N_5O_3.2HCl$

Chemical Structure:



Molecular Weight: 314.17 g/mol

Appearance: Off-white to pale yellow powder

Solubility: Sapropterin dihydrochloride is freely soluble in water and very slightly soluble in methanol.

Sapropterin dihydrochloride is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the final products.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product(s), along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 18 months, with the storage conditions ‘This medicinal product does not require any special temperature storage conditions. Keep the bottle tightly closed and store in the original package to protect from moisture and light.’, is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of sapropterin dihydrochloride are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology

No new pharmacology data were provided, and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for this application.

III.4 Toxicology
No new toxicology data were provided, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of an already authorised product, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a Marketing Authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of sapropterin dihydrochloride are well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics
In support of the application, the applicant submitted the following bioequivalence study.

Bioequivalence study (single-dose, fed conditions)
This was an open label, randomised, single-dose, two treatment, two period, two sequence, crossover bioequivalence study comparing the test product Sapropterin dihydrochloride 100 mg Soluble Tablets with the reference product Kuvan 100 mg soluble tablets in normal, healthy, adult, male, human subjects under fed conditions.

After an overnight fast, subjects were administered a single dose (700 mg; 1 x 7 tablets) of either the test or reference product with 240 ml of water under fed conditions (30 minutes after the intake of a standard high-fat high-calorie breakfast). Fasting was maintained until 5 hours after dosing. Blood samples were taken pre-dose and up to 48 hours post dose, with a washout period of 7 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Table 1 Statistical Summary of the comparative Bioavailability data for Sapropterin (Tetrahydrobiopterin, BH4) Baseline Corrected

Pharmacokinetic Parameter(s)	Test Geometric least square Mean	N	Reference Geometric least square Mean	N	Test/ Reference Ratio (%)	90 % C.I (%)		Intra CV (%)
						Lower	Upper	
$AUC_{(0-t)}$	334.71	38	323.45	38	103.48	96.77	110.65	17.41
C_{max}	57.79	38	58.48	38	98.82	92.04	106.09	18.48

Table 2 Statistical Summary of the comparative Bioavailability data for Sapropterin (Tetrahydrobiopterin, BH4) Baseline Uncorrected ~ supportive data

Pharmacokinetic Parameter(s)	Test Geometric least square Mean	N	Reference Geometric least square Mean	N	Test/ Reference Ratio (%)	90 % C.I (%)		Intra CV (%)
						Lower	Upper	
$AUC_{(0-t)}$	362.59	38	353.06	38	102.70	95.80	110.10	18.07
C_{max}	58.42	38	59.14	38	98.78	92.07	105.98	18.29

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for this application and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with this application and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study no new safety data were submitted with this application.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulations 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of a Marketing Authorisation is recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL 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

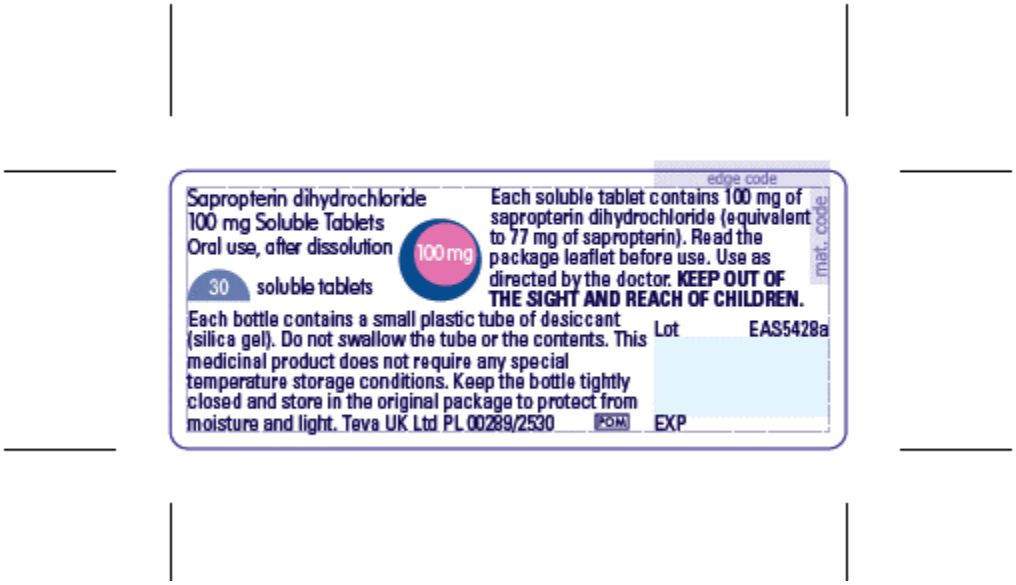
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with sapropterin dihydrochloride is

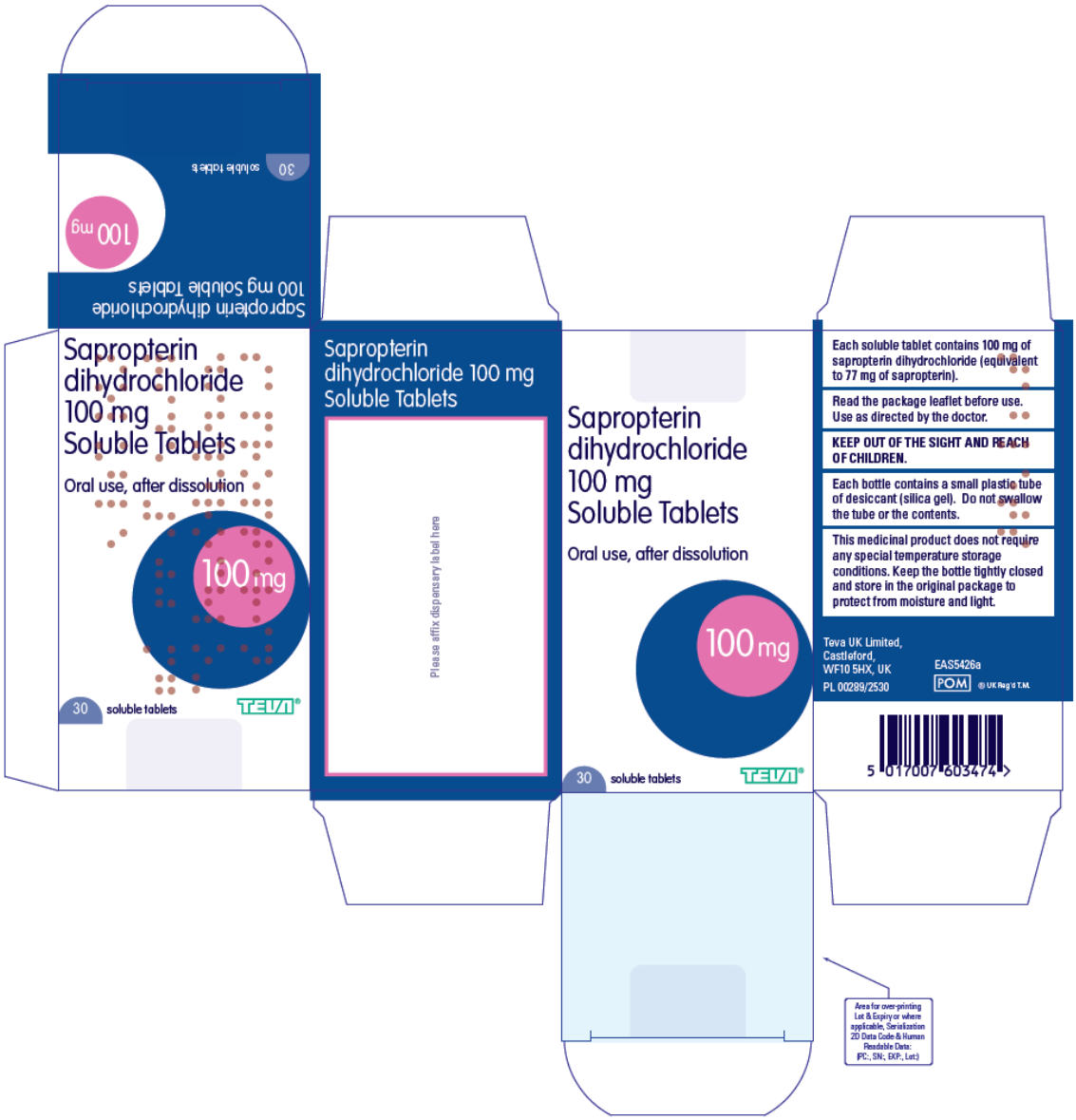
considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), PIL and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

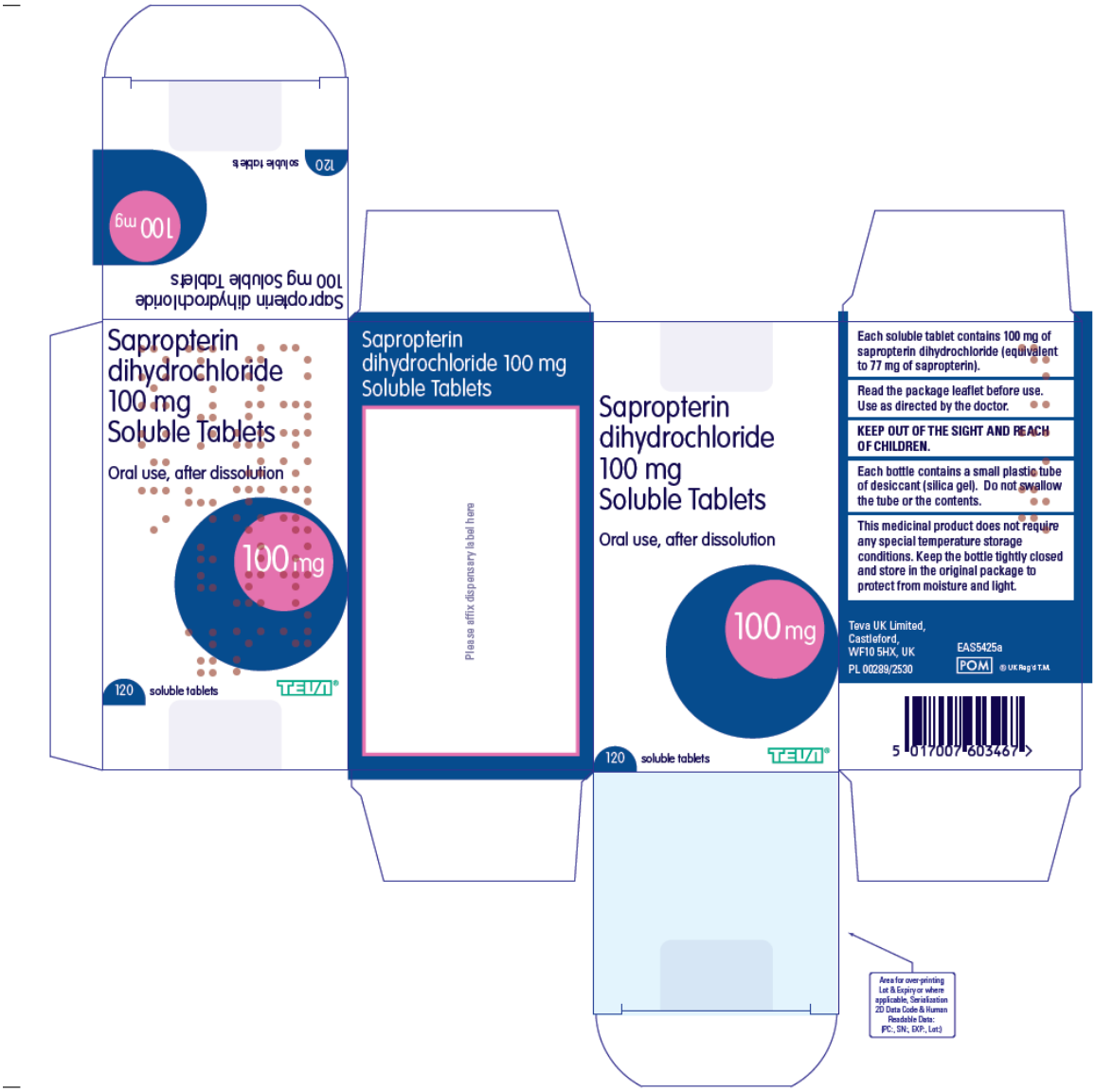
In accordance with legal requirements, the current approved UK versions of the SmPC and PILs for this product are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.




Sapropterin dihydrochloride 100 mg Soluble Tablets
Oral use, after dissolution
100 mg
30 soluble tablets
Sapropterin dihydrochloride 100 mg Soluble Tablets
Please affix dispensary label here
Each soluble tablet contains 100 mg of sapropterin dihydrochloride (equivalent to 77 mg of sapropterin).
Read the package leaflet before use. Use as directed by the doctor.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.
Each bottle contains a small plastic tube of desiccant (silica gel). Do not swallow the tube or the contents.
This medicinal product does not require any special temperature storage conditions. Keep the bottle tightly closed and store in the original package to protect from moisture and light.
Teva UK Limited, Castleford, WF10 5HX, UK
PL 00289/2530
EAS5426a
POM
5 017007 603474
Area for over-printing Lot & Expiry or where applicable, Serialisation 2D Data Code & Human Readable Data: (PC:, SN:, EXP:, Lot:)


edge code
Sapropterin dihydrochloride 100 mg Soluble Tablets
Oral use, after dissolution
100 mg
120 soluble tablets
Each soluble tablet contains 100 mg of sapropterin dihydrochloride (equivalent to 77 mg of sapropterin). Read the package leaflet before use. Use as directed by the doctor. KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.
mat. code
Each bottle contains a small plastic tube of desiccant (silica gel). Do not swallow the tube or the contents. This medicinal product does not require any special temperature storage conditions. Keep the bottle tightly closed and store in the original package to protect from moisture and light. Teva UK Ltd PL 00289/2530
POM
Lot EAS5453a
EXP


Sapropterin dihydrochloride 100 mg Soluble Tablets
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5 017007 603467
Area for over-printing Lot & Expiry or where applicable, Serialization 2D Data Code & Human Readable Data: (PC., SN:, EXP:, Lot:)

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**