16 December 2021
EMA/2232/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sapropterin Dipharma

International non-proprietary name: sapropterin

Procedure No. EMEA/H/C/005646/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Sapropterin Dipharma
Applicant:	Dipharma B.V. Prins Bernhardplein 200 1097 JB Amsterdam NETHERLANDS
Active substance:	Sapropterin dihydrochloride
International Nonproprietary Name/Common Name:	sapropterin
Pharmaco-therapeutic group (ATC Code):	OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS, Various alimentary tract and metabolism products (A16AX07)
Therapeutic indication(s):	Sapropterin Dipharma 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 section 4.2). Sapropterin Dipharma 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 section 4.2).
Pharmaceutical form(s):	Powder for oral solution; Soluble tablet
Strength(s):	100 mg and 500 mg
Route(s) of administration:	Oral use
Packaging:	bottle (HDPE) and sachet (PET/Alu/PE)
Package size(s):	120 tablets, 30 tablets and 30 sachets

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List of abbreviations

AAS	Atomic Absorption Spectrometry
AE	adverse event
ANDA	Abbreviated New Drug Application (ANDA) is an application for a U.S. generic drug approval
ANOVA	analysis of variance
AP	Applicant's Part (or Open Part) of a ASMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
AUC	the area under the plasma concentration
$AUC_{\_\%Extrap\_obs}$	residual area in percentage
$AUC_{0-\infty}$	the area under the plasma concentration - time curve from time 0 to infinity
AUC_{0-t}	the area under the plasma concentration - time curve from time 0 to t hours
BE	Bioequivalence
BH4	Tetrahydrobiopterin
CEP	Certificate of Suitability of the EP
CFU	Colony Forming Units
CHMP	Committee on Human Medicinal Products
CMS	Concerned Member State
CoA	Certificate of Analysis
GC	Gas Chromatography
CQA	Critical Quality Attribute
CRS	Chemical Reference Substance (official standard)
DoE	Design of experiments
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DP	Decentralised (Application) Procedure
DPM	Drug Product Manufacturer
DSC	Differential Scanning Calorimetry
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EP	European Pharmacopoeia
ERA	environmental risk assessment
EU	European Union
FCR	Functional Related Characteristics
FPM	Finished Product Manufacturer
GCP	good clinical practice
GLP	good laboratory practice
HCT	Hydrochlorothiazide
HDPE	High Density Polyethylene
HPA	Hyperphenylalaninaemia
HPLC	High performance liquid chromatography
HT	Holding time

IPC	In-process control
ICP-MS	Inductively coupled plasma mass spectrometry
IR	Infrared
IU	International Units
LC/MS/MS	liquid chromatography coupled with tandem mass spectrometry
LDPE	Low Density Polyethylene
LOA	Letter of Access
LOD	Limit of Detection
LOQ	Limit of Quantitation
LoQ	List of Questions
LoQ	list of questions
LT	Less than
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MEB	Medicines Evaluation Board
MO	Major Objection
MS	Mass Spectrometry
NaOH	Sodium Hydroxide
ND	Not detected
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
OOS	Out of Specifications
PDE	Permitted Daily Exposure
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PK	Pharmacokinetic
PKU	Phenylketonuria
PL	package leaflet
PP	Polypropylene
PSD	Particle size distribution
PSMF	Pharmacovigilance System Master File
PVC	Poly vinyl chloride
QbD	Quality by design
QOS	Quality Overall Summary
QPPV	Qualified Person Responsible For Pharmacovigilance
QTPP	Quality target product profile
RH	Relative Humidity
RMP	risk management plan
RMS	Reference Member State
RP	Restricted Part (or Closed Part) of an ASMF
rpm	rotation per minute
RRT	Relative retention time
RSD	Relative standard deviation
SD	standard deviation
SmPC	summary of product characteristics
SPC	Summary of Product Characteristics

$t_{1/2}$	the elimination or terminal half-life
TGA	Thermo-Gravimetric Analysis
T_{max}	time of the maximum measured plasma concentration
USP/NF	United States Pharmacopoeia/National Formulary
UV-VIS	Ultraviolet-Visible
XRPD	X-Ray Powder Diffraction
λ_z	first order rate constant associated with the terminal portion of the curve

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Dipharma B.V. submitted on 4 January 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Sapropterin Dipharma, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 May 2020.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is

composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Kuvan instead of non-clinical and clinical unless justified otherwise.

The chosen reference products are:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 6/8/10 years in the EEA:

- Product name, strength, pharmaceutical form: Kuvan, 100 mg, Soluble tablet
- Marketing authorisation holder: BioMarin International Limited
- Date of authorisation: 2/12/2008
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/08/481/001-002
-

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 6/8/10 years in the EEA:

- Product name, strength, pharmaceutical form: Kuvan, 100 mg and 500 mg, Powder for oral solution
- Marketing authorisation holder: BioMarin International Limited
- Date of authorisation: 2/12/2008
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/08/481/004-005

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Kuvan, 100 mg, Soluble tablet
- Marketing authorisation holder: BioMarin International Limited
- Date of authorisation: 2/12/2008
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/08/481/001-002

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Kuvan, 100 mg and 500 mg, Powder for oral solution
- Marketing authorisation holder: BioMarin International Limited
- Date of authorisation: 2/12/2008
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/08/481/004-005

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Kuvan, 100 mg, Soluble tablet
- Marketing authorisation holder: BioMarin International Limited
- Date of authorisation: 2/12/2008
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/08/481/002
- Bioavailability study number(s): AZ/BE/07/19/10

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Frantisek Drafi

The application was received by the EMA on	4 January 2021
The procedure started on	21 January 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	12 April 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	23 April 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	20 May 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	3 August 2021
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	20 September 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 October 2021
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	14 October 2021
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	16 November 2021
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	1 December 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Sapropterin Dipharma on	16 December 2021
The CHMP adopted a report on similarity of Sapropterin Dipharma with Palynziq) on (Appendix on similarity)	16 December 2021

2. Scientific discussion

2.1. Introduction

This centralised application for a marketing authorisation concerns a generic application according to article 10(1) of Directive 2001/83/EC for Sapropterin Dipharma (sapropterin dihydrochloride), soluble

tablets, 100 mg and powder for oral solution, 100 mg and 500 mg. Application has been submitted by the applicant Dipharma B.V., Netherlands.

The reference medicinal product is Kuvan available in the form of 100 mg soluble tablets and 100 mg and 500 mg powder for oral solution (MAA No: EU/1/08/481, BioMarin International Limited, Ireland) authorised on 02 December 2008 in the EU. It was originally designated as an orphan medicinal product on 8 June 2004 (EU/3/04/199). Kuvan was withdrawn from the Community register of orphan medicinal products in December 2020 at the end of the 12-year period of market exclusivity.

Sapropterin Dipharma has the same quantity of the active substance, same pharmaceutical forms, strengths and route of administration as the chosen reference medicinal products.

In addition, the proposed indications and posology are in line with the chosen reference medicinal products.

One bioequivalence (BE) study has been performed using the reference medicinal product, Kuvan. The test product (Sapropterin 100 mg soluble tablets, Batch number: P05G19-238) and the reference product (Kuvan® 100 mg, soluble tablets, Batch number: L141448, sourced from Ireland) were compared in healthy adult subjects in fed condition (Study No. DPH01- 2019-001-BE).

The applicant is requesting a biowaiver for 100 and 500 mg powder for oral solution.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented in two dosage forms, as a powder for oral solution and as soluble tablets. The powder for oral solution contains 100 mg or 500 mg of sapropterin dihydrochloride as active substance; the soluble tablets contain 100 mg of sapropterin dihydrochloride as active substance.

Other ingredients are:

Powder for oral solution: mannitol (E421), potassium citrate (E332), sucralose (E955), ascorbic acid (E300)

Soluble tablet: mannitol (E421), crospovidone type A, copovidone K28, ascorbic acid (E300), sodium stearyl fumarate, riboflavin (E101) and anhydrous colloidal silica (E551).

The powder for oral solution is available in polyethylene terephthalate, aluminium, polyethylene laminate sachet, heat sealed on four sides. An internal tear notch is located in the corner of the sachet to facilitate opening of the sachet, as described in section 6.5 of the SmPC.

The soluble tablets are available in high-density polyethylene (HDPE) bottle with child-resistant closure with screw cap containing desiccant (silica), as described in section 6.5 of the SmPC.

2.3. Active substance

General information

The documentation on the active substance is presented using an Active Substance Master File (ASMF) procedure.

The chemical name of sapropterin dihydrochloride is (6R)-2-amino-6-[(1R,2S)-1,2-dihydroxypropyl]-5,6,7,8-tetrahydropteridin-4-one dihydrochloride corresponding to the molecular formula $C_9H_{15}N_5O_3 \cdot 2HCl$. It has a molecular mass of 314.17 g/mol and the following structure:

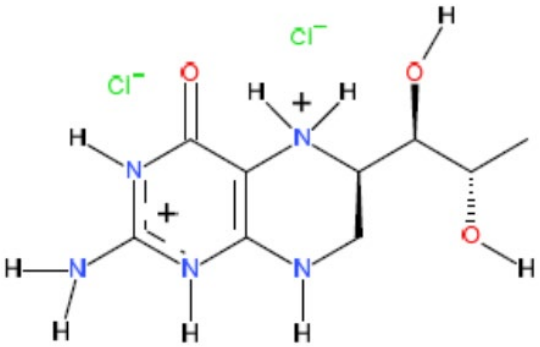

Figure 1: active substance structure

The chemical structure of sapropterin dihydrochloride was elucidated by a combination of number of methods, i.e. IR, ^{1}H-NMR, ^{13}C-NMR spectroscopy, HPLC, DSC, mass spectrometry and elementary analysis. The solid state properties of the active substance were measured by XRPD.

The sapropterin dihydrochloride is a white crystalline odourless deliquescent powder. It is soluble in solvents (mixture alcohol-water, DMSO, DMF, lightly soluble in ethanol) and water (pH independent solubility > 600 mg/mL).

Sapropterin dihydrochloride exhibits stereoisomerism due to the presence of three chiral centres. In response to a major objection (MO), it has been demonstrated that the manufacturer consistently synthesises the 6R, 1'R, 2'S form, which is the same form as used in the reference product. Enantiomeric purity is controlled routinely by chiral XRPD profile, at release, and optical rotation, both at release and during stability. Tautomerism cannot occur for the protonated (dihydrochloride salt) active substance. Stability data support that only one stereoisomer is present in the active substance through its retest time.

Polymorphism has been observed for sapropterin dihydrochloride. A total fifteen forms have been identified, including polymorphic forms (A, B, F, J, K), hydrates (C, D, E, H, O) and solvates (G, I, L, M, N), as reported in literature. Form B is a thermodynamically stable crystalline anhydrate and it can be specifically identified by X-ray powder diffraction. Sapropterin dihydrochloride form B is consistently manufactured by the proposed manufacturing process as demonstrated by data. Additionally, given that the finished products are formulated as soluble pharmaceutical forms, that will be dissolved prior to administration, and in view of the high aqueous solubility of the active substance, the existence of polymorphism is not a source of concern.

Manufacture, characterisation and process controls

The active substance is manufactured by one active substance manufacturer.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Sapropterin dihydrochloride is synthesized using commercially available well-defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Potential and actual impurities were well discussed with regards to their origin and characterised.

Four potential genotoxic impurities arise from the synthesis of sapropterin dihydrochloride are identified. The manufacturing process of sapropterin dihydrochloride ensures effective purging of all potentially genotoxic impurities discussed. The absence of benzene in the final active substance has been confirmed by analysis of four industrial batches. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

The commercial manufacturing process for the active substance started before the clinical development program. The active substance used in the clinical program is unchanged.

The active substance is packaged in double PE bags (with silica gel in between), outer aluminium bag and HDPE drums. PE bags comply with EC 10/2011 as amended.

Specification

The active substance specification, includes tests for: appearance, specific optical rotation, pH, identity (HPLC, XRPD, chloride test), loss on drying (USP/Ph. Eur.), residue on ignition (USP), chloride content (titration), assay (titration, HPLC), impurities (HPLC), residual solvents (GC), platinum content (ICP-MS) and particle size distribution (laser diffraction).

The active substance specification as used by the finished product manufacturer, are the same as the specification applied by the active substance manufacturer, with the exception that a three-tier limit for the particle size distribution (PSD) has been implemented during the procedure, as PSD may adversely impact product segregation within the blend; the limit for residual platinum has been removed as Pt is controlled by the active substance manufacturer only.

Limits for impurities have been set in line with ICH Q3A. During the procedure, a specification limit for residual solvents used in the manufacturing process of sapropterin dihydrochloride active substance has been implemented into specification. Absence for a test on microbiological quality in the active substance specification has been justified as the manufacturing process assures that microbial growth is avoided, since low pH is maintained through the manufacturing method and the solvent isopropyl alcohol, which has antimicrobial properties, is used in the last manufacturing process steps of the active substance, prior to drying.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on three full scale commercial batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three full scale commercial batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 24 months under long term conditions (25°C / 60% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. The following parameters were tested: appearance, identification (HPLC, XRPD), loss on drying, assay (titration), assay (HPLC) and related substance. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications.

Photostability testing following the ICH guideline Q1B was performed on one batch. Results on stress conditions (basic conditions: 1 M NaOH; acidic conditions: 1 M HCl; oxidative conditions: 3% H_2O_2; warm conditions: 105°C for 12 h + 12 h; light exposure for 24 h, UV 254 nm, 24 h) were also provided on one batch. The provided results from photostability study demonstrated that sapropterin dihydrochloride is sensitive to exposure to light with respect to the appearance of the powder; no significant modification of the purity of the product occurs due to exposure to light. The container closure system is adequate to prevent changes in the appearance of the powder.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months when stored in the proposed container. The active substance should be stored in tight, light resistant container with no special temperature storage conditions requirements.

2.4. Finished medicinal product - Sapropterin Dipharma 100 mg soluble tablets

Description of the product and Pharmaceutical development (soluble tablets)

White to off-white, approximately 10 mm x 3.65 mm, round tablet debossed with "11" on one side and score line on the other side. The score line is not intended for breaking the tablet.

No overages are included in finished product.

The finished product has been developed to be a generic equivalent to the reference medicinal product Kuvan 100 mg soluble tablets.

The majority of the excipients are the same in both test and reference product. The main differences between the test and reference product were the replacement of the binder calcium hydrogen phosphate with copovidone and the addition of a very small amount of the glidant silica colloidal anhydrous. No safety relevance and influence on bioavailability are expected in view of the difference in binder and glidant type between the test and reference product. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The choice of the excipients, including the antioxidant ascorbic acid, is supported by pre-formulation studies and stability data demonstrating the compatibility and suitability of the excipient with the active substance sapropterin dihydrochloride. A satisfactory description of the formulation optimisation, to address issues of adhesion of the blend to the punches of the tableting equipment, ensuring that the correct disintegration time has been maintained.

The pharmaceutical development of the finished product contains QbD elements. The objective was to prepare a soluble tablet being essentially similar to the reference medicinal product; the quality target product profile (QTPP) was defined based on the properties of the active substance, characterisation of the reference product (PK, physicochemical characterisation and *in vitro* dissolution) and consideration of the reference product label and intended patient population. The critical quality attributes identified were assay, dosage uniformity, disintegration and dissolution, loss on drying and degradation products. A risk assessment of the active substance attributes (solid state form, particle size distribution, hygroscopicity, solubility, residual solvents, process impurities, chemical stability and flow

properties) was performed to evaluate the impact that each attribute could have on the finished product CQAs.

As sapropterin dihydrochloride is considered a highly soluble BCS Class III compound (high solubility and low permeability), particle size is indicated as not critical material attribute for the soluble tablets; however, a specification limit has been set.

The active substance polymorphic form (form B) stability in the finished product and during storage has been demonstrated by experimental data.

In response to a MO raised on the stereoisomer of the active substance and finished product, the stability of the desired 6R, 1'R, 2'S stereoisomer has been demonstrated for the finished product through its shelf life.

Due to the hygroscopicity of the active substance, direct tableting was chosen as the manufacturing process for the proposed finished product, which includes sifting, blending, lubrication, compression and packaging. The manufacturing development has been evaluated through the use of risk assessment to identify critical process parameters. The critical process parameters have been adequately identified.

The conditions of the selected dissolution method used for QC check are: 900 ml of 0.1 N HCl as dissolution medium, paddle apparatus (II), 50 rpm at 37°C. The active substance is highly soluble in water and over the physiological pH range (pH 1.2 to 6.8), its solubility is pH independent, as demonstrated by solubility tests. The stability of active substance in solution decreases significantly with increasing the pH of the medium (above pH 3.1), thus the choice of 0.1 N HCl is appropriate. Due to high solubility, the deliberate alteration of formulation changes in critical excipients (binder, disintegrant and lubricant) and/or challenging process parameters (lubrication time, compression speed and compression force) did not lead to a dramatic change in dissolution profile of sapropterin soluble tablet. Thus, the discriminatory power of the dissolution method cannot be demonstrated. However, a disintegration test is included in the sapropterin soluble tablet specification, whose compliance with set limit confirms the complete disintegration of soluble tablet into water. The suitability of the dissolution method has been demonstrated in response to a MO raised during the procedure.

Bioequivalence between the reference product Kuvan 100 mg soluble tablets approved and marketed in EU (batch no. L141448, expiry date 11/2021), and one full production scale batch of Sapropterin Dipharma 100 mg soluble tablets manufactured by the proposed finished product manufacturer with the proposed formulation and manufacturing process was demonstrated in one clinical study under fed conditions. This is further discussed in the clinical part of the report.

An in vitro comparative dissolution test was performed for the test (biobatch) and the reference products used in *in vivo* bioequivalence study, in accordance to the Guideline on Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98, Rev. 1), was performed using the chosen dissolution conditions (900 ml dissolution medium, paddle apparatus (II), 50 rpm at 37°C) at three different pHs (pH 1.2; pH 4.5 in acetate buffer with 0.1% ascorbic acid to improve the stability of the product; pH 6.8 in phosphate buffer with 0.1% ascorbic acid to improve the stability of the product). In addition, comparative dissolution data were also obtained on first three full production scale batches; when tested at three different pHs (pH 1.2; pH 4.5 in acetate buffer with 0.1% ascorbic acid to improve the stability of the product; pH 6.8 in phosphate buffer with 0.1% ascorbic acid to improve the stability of the product) at the chosen dissolution conditions (900 ml, 50 rpm, paddle apparatus II, 37°C). The *in vitro* dissolution studies show comparable profiles as more than 85% of the active substance is dissolved within 15 minutes. During the procedure, it was confirmed that the biobatch contained the desired stereoisomer of the reference product.

The organoleptic properties of the formulation have been satisfactorily discussed. In view of the physical chemical characteristics of the active substance in solution and taking into account guidance documents published after the approval date of the reference product (e.g. Guideline on pharmaceutical development of medicines for paediatric use EMA/CHMP/QWP/805880/2012 Rev. 2 and Administration of oral immediate release medicinal products through enteral feeding tubes December 2018), some details are missing from the SmPC of both pharmaceutical forms that should be included and, where necessary, should be supported by compatibility studies for both finished products (powder for oral solution and soluble tablets); for future development, the applicant is recommended to investigate the effect of mixing the finished products with common food or drinks, as the absence of recommendations on mixing with food or drinks in the SmPC will not assure that caregivers will not employ this method in order to administer a medicinal product. The applicant is also recommended to investigate the feasibility of administering the product through enteral feeding tubes.

The primary packaging of soluble tablets is high-density polyethylene (HDPE) bottle with child-resistant closure with screw cap containing desiccant (silica). Each bottle contains 30 or 120 soluble tablets. The material complies with EC requirements. The child-resistant cap is compliant with ISO 8317:2015. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls (soluble tablets)

The manufacturing process of soluble tablets consists of four main stages: dispensing (step 1); sifting, blending and lubrication (steps 2-6); tableting (step 7); primary and secondary packaging (step 8). The process is considered to be a standard manufacturing process.

Process validation of Sapropterin Dipharma 100 mg soluble tablets was performed on three full scale consecutive batches of bulk product corresponding to six batches of packaged finished product. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification (soluble tablets)

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance (visual), average weight (Ph. Eur.), disintegration time, average weight (Ph. Eur.), disintegration time (Ph. Eur.), hardness (in-house), loss on drying (Ph. Eur.), identification of sapropterin dihydrochloride (UV and HPLC), identification of colourant for riboflavin (UV - VIS), identification of ascorbic acid (UV and HPLC), uniformity of dosage units (mass variation, Ph. Eur.), dissolution (HPLC, In-house/Ph. Eur. 2.9.3), related substances (HPLC), assay of sapropterin dihydrochloride (HPLC), content of ascorbic acid (HPLC), and microbiological tests (Ph. Eur.).

The proposed specification for the finished product is in line with ICH Q6A, where relevant.

During the procedure, the limit for dissolution test in the finished product release and shelf life specification has been tightened in line with batch data, and the limit for content of ascorbic acid has been tightened in release and shelf-life specification. The release limit and the shelf life limit for loss on drying has also been tightened.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on three batches using a validated ICP-MS method were provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment

and the presented batch data, it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three industrial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product (soluble tablets)

Stability data from six industrial scale batches of finished product stored for up to eighteen months under long term conditions (25°C / 60% RH) and for up to six months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. The batches of Sapropterin Dipharma 100 mg soluble tablets are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, disintegration time, hardness, loss on drying, dissolution, related substances, sapropterin dihydrochloride assay, content of ascorbic acid and microbial tests. The analytical procedures used are stability indicating.

All tested parameters are within the specification with storage in proposed container closure system.

In addition, one batch of the 30 tablets pack size, considered as worst case, was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. An increased in degradation products, within the acceptance criteria, was observed for the exposed samples, demonstrating the suitability of the intended packaging material against light penetration.

An in-use stability study has been performed on two finished product batches of 120 tablet pack size representing the worst case. The batches complied with the specification confirming the suitability of the intended 60 days of in-use stability. However, no in-use shelf life after first opening of the bottle is stated in the drug product information which is in compliance with the Quality of medicines Q&A Part 2 since no significant changes were observed across the stability studies.

To support the method of administration as described in the SmPC, an in-use study was conducted which demonstrates physic-chemical stability of the product for 20 minutes after dissolution.

Based on available stability data, the proposed shelf-life of 24 months as stated in the SmPC (section 6.3) is acceptable. No special storage conditions are required.

Adventitious agents (soluble tablets)

No excipients derived from animal or human origin have been used.

2.5. Finished medicinal product: 100 mg and 500 mg powder for oral solution

Description of the product and Pharmaceutical development (powder for oral solution)

The finished product Sapropterin Dipharma 100 mg and 500 mg powder for oral solution is a white to yellowish powder for oral solution; it has been developed to be a generic equivalent to the reference medicinal product Kuvan 100 mg powder for oral solution and Kuvan 500 mg powder for oral solution. No overages are included in the finished product.

The qualitative composition is the same for the test and reference product. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The choice of the excipients, including the antioxidant ascorbic acid, is supported by pre-formulation studies and stability data demonstrating the compatibility and suitability of the excipient with the active substance sapropterin dihydrochloride.

The pharmaceutical development of the finished product contains QbD elements. The objective was to prepare a powder for oral solution being essentially similar to the reference medicinal product; the quality target product profile (QTPP) was defined based on the properties of the active substance, physicochemical characterisation of the reference product and consideration of the reference product label and intended patient population. The formulation and manufacturing development have been evaluated through the use of risk assessment to identify the critical product quality attributes and critical process parameters. The critical quality attributes identified were identification, assay, uniformity of dosage units (UOD), impurities, moisture content and microbial limits. A risk assessment of the active substance attributes (solid state form, particle size distribution, solubility, moisture content and flow properties) was performed to evaluate the impact that each attribute could have on the finished product CQAs.

The active substance polymorphic form (form B) stability in the finished product and during storage has been demonstrated by experimental data.

In response to a MO raised on the stereoisomer of the active substance and finished product, the stability of the desired 6R, 1'R, 2'S stereoisomer has been demonstrated for the finished product through its shelf life.

Particle size distribution may impact product segregation within the blend, hence on uniformity of dosage units and assay. Hence, a specification limit has been set for the active substance PSD (for D10, D50, D90) in line with batch data.

The chosen manufacturing method consists of direct blending of the dispensed finished product components and packaging.

An *in vitro* comparative dissolution test was performed for three process validation batches per strength of the test product versus one batch per strength of the reference product, in accordance to the Guideline on Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98, Rev. 1). The profiles were generated at three different pHs (pH 1.2; pH 4.5 in acetate buffer and with 0.1% ascorbic acid to

improve the stability of the product; pH 6.8. in phosphate buffer with 0.1% ascorbic acid to improve the stability of the product) using the chosen dissolution conditions (900 ml dissolution medium, paddle apparatus (II),50 rpm at 37°C). The *in vitro* dissolution studies show comparable profiles as more than 85% of the active substance is dissolved within 15 minutes. Biowaiver of 100 mg and 500 mg powder for oral solution has been applied. Since the product meets the general requirements according to Guideline on Investigation on Bioequivalence, the biowaiver for 100 mg and 500 mg powder for oral solution can be accepted.

In view of the physical chemical characteristics of the active substance in solution and taking into account guidance documents published after the approval date of the reference product (e.g. Guideline on pharmaceutical development of medicines for paediatric use EMA/CHMP/QWP/805880/2012 Rev. 2 and Administration of oral immediate release medicinal products through enteral feeding tubes December 2018), some details are missing from the SmPC of both pharmaceutical forms that should be included and, where necessary, should be supported by compatibility studies for both finished products (powder for oral solution and soluble tablets); for future development, the applicant is recommended to investigate the effect of mixing the finished products with common food or drinks, as the absence of recommendations on mixing with food or drinks in the SmPC will not assure that caregivers will not employ this method in order to administer a medicinal product. The applicant is also recommended to investigate the feasibility of administering the product through enteral feeding tubes.

The primary packaging of powder for oral solution is polyethylene terephthalate, aluminium, polyethylene laminate sachet, heat sealed on four sides. Each carton contains 30 sachets. An internal tear notch is located in the corner of the sachet to facilitate opening of the sachet. The materials comply with EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls (powder for oral solution)

The manufacturing process of powder for oral solution consists of four main steps: dispensing (step 1); first co-sieving and blending (step 2); second sieving and blending (step 3); primary and secondary packaging (step 4). The process is considered to be a standard manufacturing process.

Process validation of Sapropterin Dipharma 100 mg and 500 mg powder for oral solution was performed on three full scale consecutive batches per strength of the finished product. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification (powder for oral solution)

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: appearance of the powder (visual testing), appearance of sachet (visual testing, average weight (Ph.Eur.), loss on drying (Ph. Eur. 2.2.32), pH of the solution (in-house), identification of Sapropterin dihydrochloride (UV and HPLC), identification of ascorbic acid (UV and HPLC), uniformity of dosage units (content uniformity, Ph. Eur.), assay of sapropterin dihydrochloride (HPLC), content of ascorbic acid (HPLC), reconstitution time (in-house), seal test (in-house), and microbiological tests (Ph. Eur.).

The proposed specification for the finished product is in line with ICH Q6A, where relevant.

During the procedure, the limit for dissolution test in the finished product release and shelf life specification has been tightened in line with batch data. The limit for content of ascorbic acid has been

tightened in the shelf-life specification. The limit for total impurities in the finished product specification has been tightened at release and during shelf life.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on three batches using a validated ICP-MS method were provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data, it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all potential root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) N° 726/2004 for nitrosamine impurities in human medicines (EMA/425645/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three industrial scale batches of both strengths confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product (powder for oral solution)

Stability data from three industrial scale batches of both strengths of finished product stored for up to eighteen months under long term conditions (25°C / 60% RH) and for up to six months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. The batches of Sapropterin Dipharma 100 mg and 500 mg powder for oral solution are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, appearance of sachets, loss on drying, related substances, sapropterin dihydrochloride assay, content of ascorbic acid, seal test and microbial tests. The analytical procedures used are stability indicating.

All tested parameters are within the specification with storage in proposed container closure system. No trend is visible during whole testing period for any of the tested parameters.

In addition, one batch of the 100 mg strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant differences between the exposed and dark samples were noted demonstrating the suitability of the intended packaging material against light penetration.

An in-use study was conducted which demonstrated physico-chemical stability of the products for 30 minutes after dissolution. Samples of three batches of each strength were dissolved in 120 ml and in 240 ml. The dissolution time was measured. Appearance of the solution, assay and related substances

were evaluated after dissolution and 30 minutes after dissolution. All acceptance criteria were fulfilled. No deterioration can be observed.

Based on available stability data, the proposed shelf-life of 24 months as stated in the SmPC (section 6.3) is acceptable. No special storage conditions are required.

Adventitious agents (powder for oral solution)

No excipients derived from animal or human origin have been used.

2.6. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. Adequate justification has been given for the choice of the QC dissolution method. Additionally, during the procedure the applicant has demonstrated that the same isomer of the reference product is consistently manufactured by the proposed active substance manufacturer used and it is stable through the retest period of the active substance and shelf life of the finished product. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. At the time of the CHMP opinion, there were two minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain the investigation of the effect of mixing the finished products with common food or drinks and the feasibility of administering the products through enteral feeding tubes. These points are put forward and agreed as recommendations for future quality development.

2.7. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.8. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation for both pharmaceutical forms:

1. The applicant is recommended to investigate the effect of mixing the finished products with common food or drinks for both finished products (powder for oral solution and soluble tablets). The absence of recommendations on mixing with food or drinks in the PI will not assure that caregivers will not employ this method in order to administer a medicinal product. The PI should be updated accordingly.
2. The applicant is recommended to investigate the feasibility of administering the products (powder for oral solution and soluble tablets) through enteral feeding tubes. The PI should be updated accordingly.

2.9. Non-clinical aspects

2.9.1. Introduction

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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.9.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Sapropterin Dipharma manufactured by Dipharma B.V. is considered unlikely to result in any significant increase in the combined sales volumes for all sapropterin containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.9.3. Conclusion on the non-clinical aspects

The CHMP considers the justifications for absence of new non-clinical and ERA data as acceptable considering the type of application (natural occurring substance).

2.10. Clinical aspects

2.10.1. Introduction

This is an application for soluble tablets and an oral solution containing sapropterin dihydrochloride 100 mg and an oral solution containing sapropterin dihydrochloride 500 mg. To support the marketing authorisation application the applicant provided the following data:

- The applicant conducted one bioequivalence study (No. DPH01- 2019-001-BE; AZ/BE/07/19/10) with cross-over design under fed conditions. This study was the pivotal study for the sapropterin 100 mg soluble tablets.

Furthermore, the applicant submitted an exemption from the requirement to perform a bioequivalence (BE) study for the oral solutions containing sapropterin dihydrochloride 100 mg and 500 mg, respectively.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

According to the proposed SmPC (section 4.1) Sapropterin Dipharma is indicated:

Sapropterin Dipharma 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 section 4.2).

Sapropterin Dipharma 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 section 4.2).

According to the proposed SmPC (section 4.2) the posology and method of administration of Sapropterin Dipharma follows the reference medicinal product:

The recommended dose is in the range of 5 to 20 mg/kg/day. In elderly and patients with renal or hepatic impairment, caution must be exercised.

The tablets should be placed in a pre-specified amount of water, stirred until dissolved and the solution should be swallowed. The solution should be drunk within 15 to 20 minutes. It is recommended to administer it together with a meal to increase the absorption.

GCP aspect

The Clinical trial was performed in accordance with GCP as claimed by the applicant.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

A BCS-based biowaiver is requested for both strengths (100 and 500 mg) of powder for oral solution. The following requirements are claimed to be fulfilled:

- sapropterin is a BCS Class III compound (Kuvan AusPAR 2011, Module 3.2.S.1.3), i.e. it satisfies the criteria regarding solubility and permeability;
- the drug products are immediate-release oral dosage forms with systemic action;
- both the test product and reference product display very rapid (≥ 85% for the mean percent dissolved within 15 minutes) *in vitro* dissolution characteristics;
- test and reference products are identical in terms of dosage form and strengths; they can also be considered identical in terms of qualitative and quantitative composition ;
- the mode of administration includes water;
- the *in vitro* bioequivalence (i.e. proof of similarity) has been assessed and confirmed by comparative *in vitro* dissolution experiments of Sapropterin Dipharma 100 mg and 500 mg powder for oral solution manufactured by Alpex Pharma SA, Switzerland versus Kuvan 100 mg and 500 mg powder for oral solution registered and available in the EU at pH=1.2, 4.5 and 6.8 on 12 dosage units, as detailed in Module 5.3.1.3; i.e., the *in vitro* dissolution studies can be considered a surrogate for an *in vivo* bioequivalence study between Sapropterin Dipharma powder for oral solution and the reference product Kuvan powder for oral solution (see from Table 1 to Table 7).

Table 1 In vitro dissolution test parameters

Apparatus	Ph.Eur. Apparatus II - Paddle
Quantity of dissolution medium	900 mL
Temperature of dissolution medium	37 ± 1°C
Dissolution medium	pH 1.2: 0.1N HCl pH 4.5: Acetate buffer with 0.1% ascorbic acid (for improving the stability of the drug substance) pH 6.8: Phosphate buffer with 0.1% ascorbic acid (for improving the stability of the drug substance)
Dosage units for each experiment	12
Rpm	50
Sampling interval	Powder for oral solution: 2.5, 5, 7.5, 10 and 15 minutes Soluble tablets: 5, 10, 15 and 20 minutes
Dissolved amount determination (analytical method)	HPLC

Table 2 Comparative dissolution of Sapropterin Dipharma powder for oral solution batches and Kuvan powder for oral solution at pH 1.2

		Dissolution pH 1.2-Average % dissolved				
		2.5 min	5 min	7.5 min	10 min	15 min
Sachets 100 mg	KUVAN-1541900	73.35	97.74	99.50	98.73	97.73
	P05H19-241	68.77	93.07	95.33	93.24	92.53
	P06H19-241	71.03	97.17	94.82	94.39	96.97
	P07H19-241	75.24	100.91	100.41	101.55	101.23
Sachets 500 mg	KUVAN-1539890	74.51	95.58	97.53	97.14	100.18
	P08H19-241	70.31	91.95	90.32	96.76	93.80
	P09H19-241	69.95	92.66	92.63	92.40	92.91
	P10H19-241	73.39	95.68	95.71	96.11	96.12

Table 3 Comparative dissolution of Sapropterin Dipharma soluble tablet batches and Kuvan 100 mg soluble tablets at pH 1.2

		Dissolution pH 1.2-Average %dissolved			
		5min	10min	15min	20min
Soluble tablets 100 mg	KUVAN- L141448	75.76	94.72	95.72	94.88
	P02G19-238	88.23	101.70	106.73	105.82
	P03G19-238	21.43	96.43	104.04	103.32
	P04G19-238	47.80	99.23	102.48	103.73

Table 4 Comparative dissolution of Sapropterin Dipharma powder for oral solution batches and Kuvan powder for oral solution in pH 4.5 acetate buffer

		Dissolution pH 4.5-Average % dissolved				
		2.5 min	5 min	7.5 min	10 min	15 min
Sachets 100 mg	KUVAN-1541900	73.51	99.53	99.63	99.84	101.29
	P05H19-241	69.38	92.53	93.48	93.29	94.27
	P06H19-241	69.61	93.04	89.93	95.64	95.58
	P07H19-241	75.56	101.42	100.28	102.64	101.43
Sachets 500 mg	KUVAN-1539890	69.55	95.23	94.29	93.91	93.96
	P08H19-241	67.78	94.63	92.20	91.00	93.41
	P09H19-241	73.71	95.72	95.52	96.13	96.09
	P10H19-241	72.23	96.52	96.04	97.43	96.13

Table 5 Comparative dissolution of Sapropterin Dipharma soluble tablet batches and Kuvan 100 mg soluble tablets in pH 4.5 acetate buffer

		Dissolution pH 4.5-Average %dissolved			
		5min	10min	15min	20min
Soluble tablets 100 mg	KUVAN-L141448	68.15	96.28	99.75	100.82
	P02G19-238	60.03	98.30	100.34	101.08
	P03G19-238	45.96	94.78	100.68	100.90
	P04G19-238	77.92	87.08	98.23	103.04

Table 6 Comparative dissolution of Sapropterin Dipharma powder for oral solution batches and Kuvan powder for oral solution in pH 6.8 phosphate buffer

		Dissolution pH 6.8-Average % dissolved				
		2.5 min	5 min	7.5 min	10 min	15 min
Sachets 100 mg	KUVAN-1541900	73.91	99.96	101.43	100.90	99.88
	P05H19-241	70.93	95.25	93.76	94.67	94.75
	P06H19-241	67.90	93.86	91.41	90.38	93.23
	P07H19-241	73.23	98.25	97.70	97.50	99.69
Sachets 500 mg	KUVAN-1539890	69.79	94.28	95.28	94.69	93.59
	P08H19-241	69.95	91.97	92.63	92.40	92.16
	P09H19-241	72.43	96.72	96.22	97.42	95.88
	P10H19-241	70.90	95.67	99.06	97.30	98.04

Table 7 Comparative dissolution of Sapropterin Dipharma soluble tablet batches and Kuvan 100 mg soluble tablets in pH 6.8 phosphate buffer

		Dissolution pH 6.8-Average %dissolved			
		5min	10min	15min	20min
Soluble tablets 100 mg	KUVAN-L141448	56.88	90.63	97.41	98.44
	P02G19-238	60.03	98.30	100.34	101.08
	P03G19-238	38.17	90.14	100.34	100.88
	P04G19-238	45.20	94.83	102.14	102.77

During the procedure, the applicant additionally submitted details of an analytical comparison with the EU reference product which showed that the compositions are not only qualitatively but also quantitatively similar.

Based on the above information, the CHMP concluded that the relevant criteria were met to support the requested BSC- biowaiver. Specifically, the additional comparative data with the EU reference product showed that the compositions of Sapropterin Dipharma and Kuvan powder for oral solution are not only qualitatively but also quantitatively similar.

Tabular overview of clinical studies

To support the application, the applicant has submitted DPH01- 2019-001-BE bioequivalence study.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Treatments	No Subjects who completed the study(No. (M/F) and Age: mean (range)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Bioequivalence	Project number: AZ/BE/07/19/10 Sponsor/MAH code: DPH01-2019-001-BE	5.3.1.2	The primary objective is to investigate the bioequivalence of Sapropterin Dipharma 100 mg soluble tablets of Dipharma SA, Switzerland (Test Product) and Kuvan® 100 mg soluble tablets of BioMarin International Limited (Reference Product) after a single oral dose administration (dose calculated by multiplying the subject's weight by 10 mg/kg and then rounding up to the next 100 mg dose) under fed conditions. The secondary objective is to assess the general safety and tolerability of Sapropterin Dipharma 100 mg soluble tablets and Kuvan® 100 mg soluble tablets.	Two-period, two-way, cross-over, open label, single dose, comparative randomized bioequivalence study.	a) **Sapropterin Dipharma** 100 mg soluble tablets (TEST). Batch No. P05G19-238. Retest date 07.2021 b) **Kuvan®** 100 mg soluble tablets (REFERENCE). Batch No. L141448. Expiry date 11.2021	29 (29 M) 34 years (23-45)	Healthy volunteers	Single dose	Complete Clinical Study Report available

2.10.2. Clinical pharmacology

2.10.2.1. Pharmacokinetics

Study DPH01-2019-001-BE (EudraCT number : AZ/BE/07/19/10) : An open label, balanced, randomized, two treatments, two sequences, two periods, single dose, cross over, bioequivalence study of Sapropterin 100 mg Soluble Tablets of Dipharma SA Switzerland and Kuvan 100 mg Soluble Tablets of BioMarin International Limited in healthy, adult, human subjects under fed condition

Methods

- **Study design**

This study is designed as comparative, randomized, balanced, two-treatment, two-period, two-sequence, two-way crossover open label bioequivalence study on healthy volunteers with a single dose administration under fed conditions. In each study period, subjects received a single oral dose of 10 mg/kg BW rounded to the next 100 mg of a sapropterin tablet (test) or a reference with 240 ml of water after an overnight fast (8 hrs). 30 minutes before dosing, the subjects received a high fat high calorie breakfast (986 kcal, 17.6% protein, 53.8% fat and 28.6% carbohydrates). Wash-out period was 2 days.

Blood samples were collected at -01.00, -00.50, 00.00 (Pre-dose) 00.50, 01.00, 01.50, 02.00, 02.50, 03.00, 03.33, 03.67, 04.00, 04.33, 04.67, 05.00, 05.50, 06.00, 08.00, 12.00, 16.00 and 24.00 hrs post-dose. Sapropterin in human plasma was analysed by LC/MS/MS.

- **Test and reference products**

Sapropterin Dipharma 100 mg, soluble tablets manufactured by Alpex Pharma SA, Switzerland (batch No: P05G19-238, manufacturing date: 07/2019, expiry date: 07/2021) has been compared to Kuvan 100mg, soluble tablets manufactured by Biomarin International Limited, Ireland (Batch No:L141448, expiry date: 11/2021).

- **Population(s) studied**

The main inclusion criteria were: healthy subjects, aged 18-45 years, BMI within 18.5-30 kg/m2, healthy by normal physical examination and medical history, normal 12-lead ECG, blood pressure and heart rate, no known allergy to the investigated product, capable of giving written informed consent prior to receiving any study medication.

The total of 30 Asian subjects were dosed and 29 completed the study. Data from these 29 subjects were used for pharmacokinetic and statistical analysis.

One subject discontinued the study. One subject was withdrawn from the study during period I due to adverse event (rash). Hence, the subject was excluded from the efficacy analysis. The handling of the drop-out is considered acceptable.

A number of protocol deviations with no significant impact on data was reported:

- There were 15 sampling time deviations ranging from 2 to 12 minutes. All were considered as not relevant as actual times were considered for the analysis;

- In one subject, the volume of withdrawn blood was 3 ml instead of 5 ml due to cannula block. This was not considered as having an impact as the volume was sufficient for bioanalysis;

- In period 2, the indwelling cannula was removed after 16 hrs sampling time point. The PK data were however still collected at 24 hrs.

-The amount of stabiliser which was added to each vial before the storage and bioanalysis was changed contrary to the protocol based on the results obtained in the method development experiments.

Concomitant medication: the only concomitant medication was administered to the subject who was excluded from the analysis.

- **Analytical methods**

Determination of sapropterin in human plasma (K_3EDTA) used a validated LC/MS/MS method.

During the bioequivalence study, blood samples were collected into tubes containing K_3EDTA as an anticoagulant, then centrifuged at 3500 rpm for about 10 minutes at 4°C. The plasma was separated into 02 aliquots in pre-labelled polypropylene tubes; 01 mL was transferred into first aliquot and remaining into aliquot 02. Polypropylene tubes were pre-labelled with subject number, study number, study period, time point and aliquot number. These samples were stored at -70+/-15°C. The longest period of sample storage was 61 days, what is covered by the long-term stability data in biological matrix for 94 days.

Total number of collected samples was 1,236. The total number of analysed analytical runs is 18, 16 out of 1,236 samples were re-assayed due to the following reasons: poor chromatography (14), above limit of quantification (1), processing error (1).

Internal standard was sapropterin-D3. A set of 8 non-zero standards with calibration range (4.283 to 1011.560 ng/mL) and 5 quality controls (4.323 to 806.064 ng/mL) were prepared on 19/07/20 and stored at a nominal temperature of -70+/-15°C.

The quality control sample data for sapropterin were assessed with between-run precision of 1.86 – 11.91% CV and accuracy of 94.38 – 107.25%.

A total number of 114 incurred samples were re-analysed, corresponding to 9% of 1,236 study samples and 99.12% of them met the acceptance criteria specified in the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009).

There were no measured sample concentrations above the calibrated upper limit of quantification. Analysis was performed in the blinded manner. Evaluation of metabolite back-conversion is not regarded as necessary. Handling of samples was adequate. There were no protocol and SOP deviations during the subject sample analysis.

The applicant however did not perform the standard addition method. See further details in the discussion on clinical aspects

In terms of polymorphism, the reference medicinal product (Sapropterin dihydrochloride) exhibits polymorphism and many crystalline forms were identified during the course of crystallisation studies. Form B is a thermodynamically stable crystalline anhydrate and it can be specifically identified by X-ray powder diffraction. Given that the finished product is formulated as soluble tablets that will be dissolved prior to administration and in view of the high aqueous solubility of the active substance, the existence of polymorphism is not a source of concern.

- **Pharmacokinetic variables**

The pharmacokinetic calculations were performed with Phoenix® WinNonlin® Version 8.1 (Certara L.P.).

Following pharmacokinetic parameters were calculated for sapropterin using standard non-compartmental methods:

Primary:

C_{max}: maximum measured plasma concentration over the time span specified

AUC_{0-t}: the area under the plasma concentration versus time curve, from time (0) to the last measurable concentration (t), as calculated by the linear trapezoidal method.

Secondary:

$AUC_{0-\infty}$: the area under the plasma concentration versus time curve from time (0) to infinity.

T_{max}: time of the maximum measured plasma concentration.

$t_{1/2}$: the elimination or terminal half-life.

K_{el}: elimination constant

$AUC_{\%Extrap\_obs}$: residual area in percentage.

- **Statistical methods**

Statistical analysis was performed using PROC GLM of SAS® Version 9.4 (SAS Institute Inc., USA).

The statistical evaluation of bioequivalence included following: analysis of variance (ANOVA) in all derived pharmacokinetic parameters, calculation of formulations ratios (point estimates) and parametric 90% confidence interval for ln-transformed AUC_{0-t} and C_{max} parameters.

ANOVA: 5 % significance level for logarithmically transformed (with the 90% confidence intervals) and untransformed data of C_{max} and AUC_{0-t}. The influence of sequence, subject (sequence), formulation and period effect was tested.

Descriptive statistics: all pharmacokinetic parameters: arithmetic mean, SD, CV%, median, min and max.

90% Confidence intervals: logarithmically transformed Test/Reference ratios had to be within 80.00-125.00% for C_{max} and AUC_{0-t}.

Handling of missing values was appropriate. There were no outliers reported.

Bioequivalence of the test product with that of the reference product under fasting condition was concluded if the 90% confidence intervals of geometric least square mean ratio of the test to reference product falls within the acceptance range of 80.00 % – 125.00% for C_{max} and AUC_{0-t} for sapropterin.

Results

Table 7 Pharmacokinetic parameters for sapropterin (non-transformed values)

	Test		Reference	
	arithmetic mean	**SD**	**arithmetic mean**	**SD**
$AUC_{(0-t)}$	3233.778	997.381	3115.558	969.040
$AUC_{(0-\infty)}$	3284.393	985.498	3144.299	972.692
C_{max}	563.505	183.257	531.158	175.711
T_{max}*	4.33	2.50-5.00	4.33	3.00-4.67

	Test		Reference	
	arithmetic mean	**SD**	**arithmetic mean**	**SD**
AUC0-t	**area under the plasma concentration-time curve from time zero to t hours**			
AUC0-∞	**area under the plasma concentration-time curve from time zero to infinity**			
Cmax	**maximum plasma concentration**			
Tmax	**time for maximum concentration (* median, range)**			

Table 8 Statistical analysis for sapropterin (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	104.38	100.03-108.91	13.16
C_{max}	106.24	100.19-112.66	9.52
*estimated from the Residual Mean Squares			

Table 9 p-values obtained from sapropterin ANOVA results after single dose administration of test and reference product

Effects	C_{max}	AUC_{0-t}	Significance
Sequence	0.7267	0.9003	Insignificant for C_{max} and AUC_{0-t}
Period	<.0001	<.0001	Significant for C_{max} and AUC_{0-t}
Treatment (Formulation)	0.0901	0.0977	Insignificant for C_{max} and AUC_{0-t}
Subjects nested within sequence	<.0001	<.0001	Significant for C_{max} and AUC_{0-t}

- **Safety data**

There was one non-serious adverse event (rash) reported by one subject following administration of test product. The subject was withdrawn from the study, the event resolved. No adverse events were reported following administration of reference product.

No serious adverse events were reported during the conduct of this study.

Individual laboratory measurements (biochemistry, haematology, immunology and urine analysis) were, in some cases, outside their reference intervals but not to an extent to be considered clinically significant by the study physician.

2.10.2.2. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.10.3. Discussion on clinical aspects

To support this generic application, the applicant submitted an exemption from the requirement to perform a bioequivalence (BE) study for the oral solutions containing sapropterin dihydrochloride 100 mg and 500 mg, respectively. The CHMP was initially concerned that bioequivalence with the EU reference medicinal product had not been demonstrated. In line with the EMA's PKWP Q&A 6.3 the waiver should follow the BCS Class 3 criteria, i.e. the compositions between the Test and EU reference products should be qualitatively the same and quantitatively similar. Based on an additional analytical comparison that was submitted during the procedure, the CHMP considered this issue adequately addressed and concluded that the composition of Sapropterin Dipharma and EU reference product were not only qualitatively but also quantitatively similar.

In addition, a bioequivalence study was conducted to support the application for Sapropterin 100 mg, soluble tablets.

The use of a relative dose 10 mg/kg rounded to the next 100 mg was based on the drafted US FDA Product Specific Guidance for Generic Drug Development of Sapropterin. This single dose was considered as safe for healthy volunteers and enough to achieve sufficient plasma concentration. The CHMP noted this was also in line with the dosing range of the reference medicinal product (5 to 20 mg/kg). The use of several tablets in a single dose could in principle introduce additional source of variability. On the other side, the CHMP agreed that such a relative dosing approach will mimic the clinical practice and that formulation effects can be still isolated as each patient will serve as its own control.

Wash-out period seemed to be long enough regarding the mean terminal half-life of 6.69 hours (range 3.91 to 16.6 hours). As the amount of sapropterin was found to be below 5% of C_{max} in the average of the pre-dose samples for each subject, it can be concluded that wash-out period was sufficient. The sampling period was sufficient to characterize the plasma concentration-time profile considering that C_{max} was achieved within the first 4 to 5 hours after administration with a meal. As no C_{max} was measured in any of the samples at the first time point, the sampling scheme has been chosen correctly.

The applicant did a baseline correction as sapropterin is an endogenous substance. First three samples (-01.00, -00.50 and 00.00) were collected for baseline correction and then averaged. Any negative values were considered as zero. This approach was in line with the EU BE guidance and thus accepted by the CHMP.

Instead of using standard addition method, the Applicant / CRO has used the Peak Area Ratio (analyte /IS) of the blank plasma to correct by subtraction the peak area ratio of the calibrators, QCs and study subject's samples. With that, the Applicant was using an instrument response below the LLOQ (even closer to LOD ~3 times S/N). Hence, the CHMP was concerned about the variability of the detection of the response using this method, that could be very unstable and inaccurate. The CHMP was of the view that the Standard Addition method completely avoids this problem because the concentration in the blank is extrapolated from concentrations that are above the LLOQ (i.e. the concentrations of the calibrators that define the calibration range). The Standard Addition method avoids having a very unstable signal too close to noise by "adding" standards (blank matrix spiked with different amounts of analyte to create a calibration curve) to move the instrument response into a less variable region.

During the validation of the bioanalytical methods, the Basal Response Ratio was determined. With these results, the applicant tried to show that their response in the blank was not so variable and the CV% of 6 replicates were acceptable. However, detection of a signal below the LLOQ was still present. Furthermore, the accuracy of that estimation was unknown. Nevertheless, additional considerations were made by the CHMP. In particular, concentrations of endogenous sapropterin were very low

compared to C_{max} after the administration of tablets (up to around 15 ng/ml versus 350-750 ng/ml). Considering that the confidence intervals for C_{max} and AUC were not marginal and that variability of endogenous sapropterin between arms was minimised by cross-over design, the CHMP did not expect this to change the conclusions of the bioequivalence study. Overall, the CHMP concluded that bioequivalence between the two formulations of sapropterin has been demonstrated. 90% CIs fall into the predefined limit 80-125%, for both AUC_{0-t} and C_{max}.

No statistically significant treatment or sequence effects were observed for the ln-transformed C_{max} and AUC_{0-t} data. The significant period effect and subjects nested within sequence effect were appropriately justified by the applicant.

Considering that the isomer form of sapropterin is the same in the test and the reference product, it is expected that they behave comparably after administration to human. Therefore, the bioanalytical results not specifying an exact isomer are acceptable.

2.10.4. Conclusions on clinical aspects

Based on the presented bioequivalence study, Sapropterin Dipharma 100 mg, soluble tablets is considered bioequivalent with Kuvan 100 mg, soluble tablets.

2.11. Risk Management Plan

2.11.1. Safety concerns

Summary of safety concerns	
Important identified risks	Hypersensitivity Hypophenylalaninaemia Interaction with vasodilators using NO metabolism, DHFR Inhibitors, 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

2.11.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.11.3. Risk minimisation measures

The safety information in the proposed product information is aligned to the reference medicinal product.

2.11.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 2 is acceptable.

2.11.5. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.11.6. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.12. Product information

2.12.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet 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.

3. Benefit-risk balance

This application concerns a generic version of sapropterin soluble tablets (100 mg) and powder for oral solution (100 mg, 500 mg). The reference product Kuvan is indicated for the treatment of hyperphenylalaninaemia (HPA) in adults and paediatric patients of all ages with phenylketonuria (PKU) and tetrahydrobiopterin (BH4) deficiency, respectively, who have been shown to be responsive to such treatment.

No non-clinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

An exemption from the requirement to perform a bioequivalence (BE) study was accepted by the CHMP for the oral solutions containing sapropterin dihydrochloride 100 mg and 500 mg, respectively.

The bioequivalence study forms the pivotal basis for Sapropterin Dipharma 100 mg soluble tablets with a single dose crossover comparative design and was conducted in healthy adults under fed state. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate. The test formulation of Sapropterin Dipharma 100 mg soluble tablets met the protocol-defined criteria for bioequivalence when compared with the Kuvan 100 mg soluble tablets. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t} and C_{max} were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Sapropterin Dipharma is not similar to Palyzinq within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Sapropterin Dipharma is favourable in the following indications:

Sapropterin Dipharma 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 section 4.2).

Sapropterin Dipharma 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 section 4.2).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- ***Periodic Safety Update Reports***

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (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 European Medicines Agency;
- 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.