Risk Management Plan

for

Sapropterin Dipharma

(Sapropterin dihydrochloride)

RMP version number: 1.1

Data lock point for this RMP: 24 June 2025

Date of (final) sign off: 27 June 2025

Rationale for submitting an updated RMP: Update to align with reference medicinal product, update MAH due to name change and update of RMP template according to GVP Module V rev. 2 guidelines.

Summary of significant changes in this RMP: Update MAH due to name change

Template:

Update of the RMP as per GVP Module V rev. 2.

Safety concerns:

Update of the list of safety concerns to remove all Important identified risks, Important potential risks and Missing information in order to align with the reference medicinal product.

Details of the currently approved RMP:

Version number: 0.2

Approved with procedure: EMEA/H/C/5646

Date of approval (opinion date): 14 July 2021

Risk Management Plan on	Date and version of the RMP
Sapropterin Dipharma / soluble tablets and powder for oral solution	27 June 2025, v1.1

QPPV name:	Dr Angela van der Salm
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV.

Risk Management Plan on	Date and version of the RMP
Sapropterin Dipharma / soluble tablets and powder for oral solution	27 June 2025, v1.1

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List of abbreviations

6*R*-BH4	6*R*-tetrahydrobiopterin
BH4	Tetrahydrobiopterin
eCTD	Electronic Common Technical Document
EEA	European Economic Area
EU	European Union
HPA	Hyperphenylalaninaemia
INN	International Non-proprietary Names
MAH	Marketing Authorisation Holder
PKU	Phenylketonuria
RMP	Risk Management Plan

Part I – Product overview

Active substances (INN or common name)	Sapropterin dihydrochloride
Pharmacotherapeutic groups (ATC Code)	Various Alimentary Tract and Metabolism Products (A16AX07)
Marketing Authorisation Holder	Dipharma Arzneimittel GmBH
Medicinal products to which this RMP refers	3
Invented name(s) in the European Economic Area (EEA)	Sapropterin Dipharma 100 mg soluble tablets Sapropterin Dipharma 100 mg powder for oral solution Sapropterin Dipharma 500 mg powder for oral solution
Marketing Authorisation procedure	Centralised Procedure
Brief description of the product	<u>Chemical class</u> Sapropterin is a synthetic version of the naturally occurring 6*R*-tetrahydrobiopterin (6*R*-BH4), which is a cofactor of the hydroxylases for phenylalanine, tyrosine and tryptophan.
	<u>Summary of mode of action</u> The rationale for administration of sapropterin dihydrochloride in patients with tetrahydrobiopterin (BH4)-responsive phenylketonuria (PKU) is to enhance the activity of the defective phenylalanine hydroxylase and thereby increase or restore the oxidative metabolism of phenylalanine in a manner 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.
	<u>Important information about its composition</u> Not applicable.
Hyperlink to the product Information	The product information is included in Module 1.3.1 of the eCTD sequence.

Indications in the EEA	Current: Sapropterin Dipharma is indicated for the treatment of: • Hyperphenylalaninaemia (HPA) in adults and paediatric patients of all ages with PKU who have been shown to be responsive to such treatment. • HPA in adults and paediatric patients of all ages with BH4 deficiency who have been shown to be responsive to such treatment.
Dosage in the EEA	Current: *PKU* The starting dose of Sapropterin Dipharma in adult and paediatric patients with PKU is 10 mg/kg body weight daily. The dose is adjusted, usually between 5 and 20 mg/kg/day, to achieve and maintain adequate blood phenylalanine levels as defined by the physician. *BH4 deficiency* The starting dose of Sapropterin Dipharma in adult and paediatric patients with BH4 deficiency is 2 to 5 mg/kg body weight daily. Doses may be adjusted up to 20 mg/kg/day.
Pharmaceutical form and strength	Current: <u>Sapropterin Dipharma 100 mg soluble tablets</u> Each soluble tablet contains 100 mg of sapropterin dihydrochloride (equivalent to 77 mg of sapropterin). <u>Sapropterin Dipharma 100 mg powder for oral solution</u> Each sachet contains 100 mg of sapropterin dihydrochloride (equivalent to 77 mg of sapropterin). <u>Sapropterin Dipharma 500 mg powder for oral solution</u> Each sachet contains 500 mg of sapropterin dihydrochloride (equivalent to 384 mg of sapropterin).
Is / will the product be subject to additional monitoring?	No

Part II – Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Since this RMP concerns a generic product, this section is not applicable.

Part II: Module SII - Non-clinical part of the safety specification

Since this RMP concerns a generic product, this section is not applicable.

Part II: Module SIII - Clinical trial exposure

Since this RMP concerns a generic product, this section is not applicable.

Part II: Module SIV - Populations not studied in clinical trials

Since this RMP concerns a generic product, this section is not applicable.

Part II: Module SV - Post-authorisation experience

Since this RMP concerns a generic product, this section is not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

Since this RMP concerns a generic product, this section is not applicable.

Part II: Module SVII - Identified and potential risks

Since this RMP concerns a generic medicinal product for which an RMP is available for the reference medicinal product, this section is not applicable.

Part II: Module SVIII - Summary of the safety concerns

Since this RMP concerns a generic medicinal product for which an RMP is available for the reference medicinal product, this section is based on the RMP from the originator.

Table SVIII.1 Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	None

Part III – Pharmacovigilance plan (including post-authorisation safety studies)

III.1: Routine pharmacovigilance activities

There are no routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.

III.2: Additional pharmacovigilance activities

Not applicable, as no additional pharmacovigilance activities such as Post Authorisation Safety Studies are planned by the MAH

III.3 Summary Table of additional Pharmacovigilance

Not applicable.

Part IV – Plans for post-authorisation efficacy studies (for generic products)

There are no imposed post-authorisation efficacy studies planned or on-going for Sapropterin Dipharma. Therefore, this Part is not applicable.

Part V – Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

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

V.1. Routine Risk Minimisation Measures

Not applicable.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Not applicable.

Part VI – Summary of the risk management plan by product

Summary of risk management plan for Sapropterin Dipharma (Sapropterin dihydrochloride)

This is a summary of the risk management plan (RMP) for Sapropterin Dipharma. The RMP details important risks of Sapropterin Dipharma, and how more information will be obtained about Sapropterin Dipharma's risks and uncertainties (missing information).

Sapropterin Dipharma's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Sapropterin Dipharma should be used.

This summary of the RMP for Sapropterin Dipharma should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Sapropterin Dipharma's RMP.

I. The medicine and what it is used for

Sapropterin Dipharma is authorised to treat high blood levels of phenylalanine in adults and children of all ages with the genetic disorders phenylketonuria (PKU) or tetrahydrobiopterin (BH4) deficiency. It contains sapropterin dihydrochloride as the active substance and it is given orally as as a soluble tablet (100 mg) or as powder for oral solution (100 or 500 mg).

Further information about the evaluation of Sapropterin Dipharma's benefits can be found in Sapropterin Dipharma's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/sapropterin-dipharma

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Sapropterin Dipharma, together with measures to minimise such risks and the proposed studies for learning more about the risks of Sapropterin Dipharma, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Sapropterin Dipharma are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Sapropterin Dipharma. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product, Kuvan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Sapropterin Dipharma.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Sapropterin Dipharma.

Part VII – Annexes

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Annex 1 – EudraVigilance interface

Not applicable.

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not applicable.

Annex 3 – Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not applicable.

Annex 4 – Specific adverse drug reaction follow-up forms

Not applicable.

Annex 5 – Protocols for proposed and on-going studies in RMP part IV

Not applicable.

Annex 6 – Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

Annex 7 – Other supporting data (including referenced material)

Not applicable.

Annex 8 – Summary of changes to the risk management plan over time

Version	Approval date Procedure	Change
1.1	Approval date: Not applicable EMEA/H/C/5646	Update RMP according to GVP Module V rev. 2 template. Update MAH due to name change Updated RMP to align with reference medicinal product. Removal of all safety concerns.
0.2	Approval date: Not applicable EMEA/H/C/5646	Updated RMP after D94 PRAC Rapporteur RMP Assessment Report. Part I: • Removal of superfluous information under 'dosage' and 'important information about its composition' Part VI: • Deleted reference to the three different formulations of Sapropterin • Updated wording to align with GVP template.
0.1	Approval date: Not applicable EMEA/H/C/5646	N/A, first version