EU RISK MANAGEMENT PLAN

FOR

Kuvan® (sapropterin dihydrochloride)

Date of Report

27 June 2024

BioMarin International Limited
Shanbally, Ringaskiddy,
County Cork
P43 R298 Ireland

RMP to be assessed as part of this application:

RMP Version Number:	v17.0
Data Lock Point for this RMP:	02 December 2022
Date of final signoff	27 June 2024

Rationale for submitting an updated RMP:

As part of the Type II variation (Procedure no. EMEA/H/C/II/0078) submitted on 30 June 2023, the Kuvan RMP was updated from version 15.2 to version 16.0 (initial submission) and version 16.1 (response to questions). A positive CHMP opinion was received for this procedure on 13 June 2024, and as per guidance, the approved EU RMP is now up-versioned to version 17.0 and submitted as part of the closing sequence to the procedure.

Summary of significant changes in this RMP:

- None

Other RMP versions under evaluation:

Not applicable

Details of the currently approved RMP:

Version number:	15.2
Approved with procedure:	EMEA/H/C/0000943/II/0073
Date of approval (opinion date):	07 July 2022

QPPV Oversight Declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV.

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LIST OF ABBREVIATIONS

ADR	adverse drug reaction
AE	adverse event
BH4	tetrahydrobiopterin
CHMP	Committee for Medicinal Products for Human Use
DHFR	dihydrofolate reductase
EEA	European Economic Area
EU	European Union
GERD	gastroesophageal reflux disease
GTN	glyceryl trinitrate
HPA	hyperphenylalaninemia
IBD	international birth date
ICH	International Conference on Harmonisation
INN	international nonproprietary name
ISDN	isosorbide dinitrate
IQ	intelligence quotient
MedDRA	Medical Dictionary for Regulatory Activities
KAMPER	Kuvan Adult Paediatric European Registry
MNT	medical nutritional therapy
NO	nitric oxide
PAH	phenylalanine hydroxylase
Phe	phenylalanine
PK	pharmacokinetics
PKU	phenylketonuria
PKUDOS	PKU Demographics, Outcomes, and Safety Registry
po	per os
PBRER	Periodic Benefit-Risk Evaluation Report
PSUR	Periodic Safety Update Report
PT	preferred term
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
UK	United Kingdom
US	United States

PART I: PRODUCT OVERVIEW

Active substance (INN or common name)	Sapropterin dihydrochloride
Pharmacotherapeutic group(s) (ATC Code)	Various Alimentary Tract and Metabolism Products A16AX07
Marketing Authorisation Holder (or Applicant)	**BioMarin International Limited** **Shanbally Ringaskiddy** **County Cork, Ireland**
Medicinal product to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Kuvan®
Marketing authorisation procedure	centralised
Brief description of the product including:	<u>chemical class</u> (6R)-2-amino-6-[(1R,2S)-1,2-dihydroxypropyl]-5,6,7,8-tetrahydro-4 (3H)-pteridinone) dihydrochloride
	<u>summary of mode of action</u> Phenylalanine (Phe) is converted into tyrosine by the enzyme phenylalanine hydroxylase (PAH) in a hydroxylating system that requires a co-factor, 6R BH4. Hyperphenylalaninemia (HPA) is a metabolic disease that can arise from genetically mutated forms of PAH with decreased enzyme activity resulting in Phenylketonuria (PKU), or deficiencies in one of the enzymes involved in the synthesis or regeneration of BH4 resulting in BH4 deficiency. 6R BH4 has been shown to partially restore oxidative metabolism of Phe in patients with PKU [Muntau 2002], possibly by increasing the expression or activity of mutant PAH [Spaapen 2003]. Therefore, the current concept of 6R BH4 administration in HPA patient with PKU aims at pharmacological modification of mutated PAH by increasing its functional activity. In HPA patients due to BH4 deficiency, replacement of 6R BH4 co-factor restores PAH activity and effectively treats HPA.
	important information about its composition NA
Hyperlink to the product information	Module 1.3.1
Indication(s) in the EEA Current (if applicable)	Kuvan is indicated for the treatment of HPA in adults and paediatric patients of all ages with phenylketonuria (PKU) who have been shown to be responsive to such treatment. Kuvan is also indicated for the treatment of HPA in adults and paediatric patients of all ages with tetrahydrobiopterin (BH4) deficiency who have been shown to be responsive to such treatment.
Proposed (if applicable)	Not applicable
Dosage in the EEA Current (if applicable)	<u>PKU</u> The starting dose of Kuvan in adult and paediatric patients with PKU is 10 mg/kg body weight once daily. The dose is adjusted, usually between 5 and 20 mg/kg/day, to achieve and maintain

	adequate blood phenylalanine (Phe) levels as defined by the physician. BH4 deficiency The starting dose of Kuvan in adult and paediatric patients with BH4 deficiency is 2 to 5 mg/kg body weight once daily. Doses may be adjusted up to 20 mg/kg/day. It may be necessary to divide the total daily dose into 2 or 3 administrations, distributed over the day, to optimise the therapeutic effect. For patients above 20 kg body weight, the calculated daily dose based on body weight should be rounded to the nearest multiple of 100 mg. Dose adjustment Blood Phe and tyrosine levels should be tested, particularly in the paediatric population, one to two weeks after each dose adjustment and monitored frequently thereafter, under the direction of the treating physician. If inadequate control of blood Phe levels is observed during treatment with Kuvan, the patient's adherence to the prescribed treatment, and diet, should be reviewed before considering an adjustment of the dose of sapropterin. Determination of response Response to this medicinal product is determined by a decrease in blood Phe. Blood Phe levels should be checked before administering Kuvan and after 1 week of use at the recommended starting dose. If an unsatisfactory reduction in blood Phe levels is observed, then the dose can be increased weekly to a maximum of 20 mg/kg/day, with continued weekly monitoring of blood Phe levels over a one-month period. The dietary phenylalanine intake should be maintained at a constant level during this period. A satisfactory response is defined as a ≥30 percent reduction in blood Phe levels or attainment of the therapeutic blood phenylalanine goals defined for an individual patient by the treating physician. Patients who fail to achieve this level of response within the described one-month test period should be considered non-responsive and should not receive treatment with Kuvan. Once responsiveness to the medicinal product has been established, the dose may be adjusted within the range of 5 to 20 mg/kg/day according to response to therapy. Method of administration Kuvan should be administered with a meal, to increase the absorption. For patients with PKU, Kuvan should be administered as a single daily dose, and at the same time each day preferably in the morning. The solution should be consumed within 30 minutes of initial dissolution. Unused solution should be discarded after administration. For instructions on dilution of the product before administration, see section 6.6. Patients above 20 kg body weight The contents of the sachet(s) should be placed in 120 to 240 ml of water and stirred until dissolved. Children up to 20 kg body weight (Use only 100 mg powder sachet(s)) The measuring devices required for dosing in children up to 20 kg body weight (ie, cup with graduations at 20, 40, 60, 80 ml; 10 ml

	and 20 ml oral syringes with graduation at 1 ml divisions) are not included in the Kuvan pack. These devices are supplied to the specialised paediatric centres for inborn errors of metabolism to be provided to the caregivers of the patients. The appropriate number of 100 mg sachet(s) should be dissolved in a volume of water depicted in Tables 1-4 in the EU SmPC based on the prescribed total daily dose. If only a portion of this solution needs to be administered, an oral syringe should be used to withdraw the volume of solution to be administered. The solution may then be transferred to another cup for administration of the medicinal product. For small infants, an oral syringe can be used. A 10 ml oral syringe should be used for administration of volumes of ≤10 ml and a 20 ml oral syringe for administration of volumes of >10 ml.
Proposed (if applicable)	Not applicable
Pharmaceutical form(s) and strengths Current (if applicable)	Soluble tablet. Off-white to light yellow soluble tablet with "177" imprinted on one face. Kuvan 100 mg soluble tablets. Each soluble tablet contains 100 mg of sapropterin dihydrochloride (equivalent to 77 mg of sapropterin). Powder for oral solution. Off-white to light yellow powder. Kuvan 100 mg powder for oral solution. Each sachet contains 100 mg of sapropterin dihydrochloride (equivalent to 77 mg of sapropterin). Kuvan 500 mg powder for oral solution. Each sachet contains 500 mg of sapropterin dihydrochloride (equivalent to 384 mg of sapropterin).
Proposed (if applicable)	Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

Module SI: Epidemiology of the indication and target population

Overview

Phenylketonuria (PKU) is a serious, inherited, autosomal recessive metabolic disorder characterised by a deficiency of the liver enzyme phenylalanine hydroxylase (PAH), in which phenylalanine (Phe) accumulates to abnormally elevated concentrations in the blood. The high blood Phe levels are toxic to the brain, resulting in significant negative effects on neurocognitive, neuropsychological, and executive function performance in adults with PKU. PAH is most abundant in the liver and catalyses the hydroxylation of Phe to tyrosine in the presence of the cofactor tetrahydrobiopterin 4 (BH4).

Prevalence of PKU

Given that PKU is a genetic condition, present throughout life, and patients have a normal life span, the incidence rates are essentially the same as the prevalence rates. A global systematic review of 85 publications reporting birth prevalence of PAH deficiency reported a weighted global estimate and regional estimates of birth prevalence overall, as well as prevalence by Phe cut-off value of the confirmatory test used for making the diagnosis (Foreman 2021).

Region	Birth Prevalence per 10,000 births (95% Confidence interval)
Europe	1.14 (0.89–1.41)
Latin America	0.98 (0.29–2.03)
Middle East/North Africa	1.18 (0.64–1.87)
North America	0.81 (0.58-1.07)
Southeast Asia	0.03 (0.02–0.05)
West Pacific	0.68 (0.43–0.98)
Global estimate[a]	0.64 (0.53–0.75)

[a] Global prevalence was calculated by weighting each region by its relative contribution to the total population.

Global birth prevalence per 10,000 births by confirmatory test Phe cut-off values were 0.96 (95% CI 0.50–1.42) for the Phe cut-off value of 360 ± 100 µmol/L; 0.50 (95% CI 0.37–0.64) for the Phe cut-off value of 600 ± 100 µmol/L; and 0.30 (95% CI 0.20–0.40) for the Phe cut-off value of 1200 ± 200 µmol/L.

Risk factors

PKU is an autosomal recessive condition that theoretically affects males and females equally, and prognosis does not vary with sex. The main risk factor for the disease is consanguinity, therefore, it is an inherited condition. For a given gene-defect, race and ethnicity do not affect the phenotypic expression of the disease as measured by Phe

tolerance (ie, the amount of Phe that can be consumed while maintaining normal Phe levels).

The main impact of race and ethnicity is on the nature of the genetic defect. Hundreds of different pathogenic variants can give rise to the PKU phenotype. These range from those with no PAH activity, low Phe tolerance and severe disease to those with genetic variants where PAH activity is modestly impaired, and Phe tolerance is higher, resulting in milder disease. In addition, the phenotype can be associated with reduced or absent PAH activity due to a deficiency of its co-enzyme, BH4.

The majority of PKU patients have poor metabolic control. According to an online survey from 81 healthcare providers in 24 European countries, patients with the more severe form of PKU (ie, untreated blood Phe levels >1,200 µmol/L) represent 66% of adults with PKU (Trefz 2015). Similarly, in a global study on the prevalence of PKU phenotype, approximately two-thirds of PKU patients (61.7%; n=9923/16092) were found to have severe PKU with blood Phe levels >1200 µmol/L (Hilllert 2020)).

Natural History

PKU is diagnosed based on elevated serum Phe level and confirmed with molecular testing (van Wegberg 2017). Most cases of PKU are identified early through newborn screening, however, if left untreated, high Phe levels during infancy and early childhood can cause profound neurocognitive and developmental defects. Elevated Phe levels in the blood and brain tissues (ie, hyperphenylalaninemia (HPA)) are toxic to the central nervous system (CNS) and can result in neurological and psychiatric pathology, and psychological and neurocognitive dysfunction (Bilder 2016; Bilder 2017; NPKUA 2014) which consequentially negatively affects patient quality of life (Moyle 2007; Pietz 1997; Smith 2000; Waisbren 1999; Gassio 2003). Specifically:

- Neurological pathology: seizures, tremor, migraine, and probably long-term neurodegeneration.
- Psychiatric: depression and anxiety.
- Psychological: mood, inattention, impulsivity, confusion, anger, reduced vitality, tiredness, and agoraphobia.
- Neurocognitive: executive function, verbal memory, inhibitory control, working memory, and cognitive flexibility.
- Executive function: planning, problem solving, information processing, bringing previous experience to bear on activities, and sustained attention.

In addition, poorly controlled blood Phe levels in older children and adults are associated with learning disabilities, attention deficit hyperactivity disorder (inattention form), and behavioral problems (ten Hoedt 2010). Therefore, the need for maintaining low blood Phe levels is important and regular monitoring of patients' serum Phe is required to ensure optimal levels are maintained.

Studies have shown that the prevalence of psychiatric and neurologic symptoms in adults with early treated PKU is higher than the general adult population in the United States (NIMH 2013). Specifically, 49% of adults with PKU reported inattention symptoms versus 4% of adults in the general population who reported attention deficit hyperactivity disorder (ADHD); 22% of adults with PKU reported anxiety symptoms versus 3% of adults in the general population who reported generalized anxiety disorder; and 18% of adults with PKU reported depression symptoms versus 7% of adults in the general population who reported major depressive disorder.

Initiation of treatment in infancy has shown to reduce the proportion of patients with irreversible brain damage, low intelligence quotient (IQ), and lower incidence of neurological and psychiatric co-morbidities. Several interventional studies have shown improvements on neuropsychiatric and executive function domains when blood Phe levels are controlled in adult PKU patients (Bilder 2016). These findings suggest that neuropsychiatric and executive functioning deficits are reversible in adults with PKU. Other recently published studies have reported widespread correlations between cognitive performance in adults with PKU and control of HPA during their life span suggesting that it is important to maintain low blood Phe throughout life (Palermo 2017; Romani 2017), to provide optimal neurocognitive function.

Comorbidities

Comorbidities of PKU relate to the condition itself (as described above) and reflect the level of treatment. In a retrospective matched cohort analysis of PKU patients with general population controls in a German research database (Trefz 2019), the prevalence ratio (PR) of comorbidities was statistically significantly higher in PKU patients vs. controls for major depressive orders (PR=2.3), chronic ischemic heart disease (PR=1.7), asthma (PR=1.7), dizziness and giddiness (PR=1.8), unspecified diabetes mellitus (PR=1.7), infectious gastroenteritis and colitis (PR=1.7), and reaction to severe stress and adjustment disorders (PR=1.6). In another medical claims database study in the United States (Burton 2018), the PR of comorbidities was also significantly higher in PKU patients vs. matched general population controls for asthma, alopecia, urticaria, gallbladder disease, rhinitis, esophageal disorders, anemia, overweight, gastroesophageal reflux disease (GERD), eczema, renal insufficiency, osteoporosis, gastritis/esophagitis, and kidney calculus.

In terms of concomitant medication, these tend to follow the comorbidities above such as the prescription of anti-depressants and anxiolytics although these conditions seem more resistant to treatment when associated with HPA. Other medication follows the management of conditions that are associated with increased age but are probably more common at an earlier age in PKU patients such as H2 antagonists and proton pump inhibitors (PPI), anti-hypertensive and lipid lowering medication and drugs to control type II diabetes; all driven by a tendency to increased obesity in the PKU population. In

the German database study (Trefz 2019), PKU patients were more likely than general population controls to be prescribed systemic antibacterials (34.7% vs. 32.8%), anti-inflammatory and antirheumatic (29.4% vs. 27.5%), renin-angiotensin agents (30.0% vs. 27.0%), acid-related disorders (29.4% vs. 20.2%) and beta-blockers (24.9% vs. 19.9%). In the US medical claims study (Burton 2018), PKU patients were more likely than the general population controls to be prescribed analgesics and antipyretics, antihypertensives, gastrointestinal agents, asthma/COPD drugs, statins, antidiabetics, thyroid hormones, antiplatelets and antianemia drugs.

Diagnosis and treatment

The European guidelines recommend diagnosing PKU as part of universal newborn screening and lifelong treatment with the exception of patients ≥12 years with untreated Phe levels <600 µmol/L; and treatment is also recommended for patients <12 years with untreated Phe levels 360 - 600 µmol/L as good metabolic control during childhood is essential to prevent cognitive function impairment in PKU (van Wegberg 2017). Similarly, the American College of Medical Genetics and Genomics (ACMG) practice guidelines recommend lifelong management of PKU, with a goal of maintaining blood Phe concentrations ≤360 µmol/L (Vockley 2014).

Currently, there are three treatment options available for patients with PKU:

- Phe- restricted diet with medical nutritional therapy (MNT) to ensure sufficient protein intake

To date, there is no cure for patients with PKU. Enzyme replacement therapy with PAH is not feasible due to the instability of PAH in plasma and the difficulty in efficiently delivering an intact, active form of the enzyme to the liver (Harding 2003; Kim 2004). Also, Phe is one of 8 essential amino acids that cannot be synthesized de novo in the human body. Thus, in the general population, physiological requirements for Phe are met exclusively by dietary protein intake.

The largest source of Phe is consumption of protein containing food products and foods sweetened with artificial sweetener. Therefore, blood Phe levels and PKU-associated symptoms are primarily managed with MNT, consisting of a low Phe diet in addition to medical food/formula to ensure sufficient protein intake that may include medical foods containing Phe-free amino acid mixtures, glycomacropeptides (GMPs), and/or large neutral amino acids (LNAAs) (Blau 2010; van Wegberg 2017). Despite supplementation of vitamins, stringent MNT has been associated with nutritional deficiencies, such as vitamin B12 and other B vitamins, vitamin D, folate, and calcium. HPA and prolonged MNT can also result in nutritional deficits (Enns 2010), dysfunctional metabolic control and bone pathology (Hoeks 2009; Camp 2014; Hvas 2006; Schulz 1995; Sarkissian 2008); and increased diabetic and cardiovascular

(CV) risk factors (eg, increased lipids, homocysteine, and body mass index [BMI]) (Moseley 2002; Macleod 2010).

The goal of low-Phe restricted diet therapy is to achieve normal neurocognitive and psychosocial functioning, and the best surrogate measure available is blood Phe concentrations with a target range. For optimal effectiveness, MNT needs to be started immediately after birth and continued for life. Stringent and onerous restriction of Phe intake thus prohibits consumption of most natural protein, such as meat, fish, chicken, eggs, nuts, beans, and dairy products. One result of these dietary restrictions is often social isolation, given the limited selection of natural foods that can be eaten, the important role of food in our social interactions, and the time burden (eg, planning, assessing, calculating, and recording food intake) required to adhere to MNT (van Wegberg 2017). Therefore, for most adults with PKU, it is universally recognised that chronic low Phe intake with MNT is not sustainable and is an unacceptable or unreasonable chronic treatment option for adults with PKU. The biggest barriers to successful maintenance of lifelong Phe-restricted dietary regimen are poor palatability, limited selection, limited availability of formulas and medical food, and social isolation.

Most PKU patients require lifelong stringent Phe-restricted diet with MNT to control blood Phe levels to help prevent complications associated with high Phe levels in the brain.

There are two pharmacological treatment options available, and they were developed to control blood Phe levels while easing or normalizing diet.

- Sapropterin dihydrochloride (Kuvan) is a synthetic version of the naturally occurring 6R-BH4, which is a cofactor of the hydroxylases for Phe, tyrosine, and tryptophan as a treatment for PKU to reduce or maintain blood Phe levels, prevent, or decrease further Phe accumulation, and increase tolerance to Phe intake in the diet; and in patients with BH4 Deficiency, to replace the deficient levels of BH4, thereby restoring the activity of PAH.

  Sapropterin in conjunction with MNT is indicated for the treatment of hyperphenylalaninemia (HPA) in adults and paediatric patients of all ages with PKU who have shown to be responsive to such treatment; and is also indicated for treatment in adults and paediatric patients of all ages with BH4 deficiency who have been shown to be responsive to such treatment.

- Pegvaliase (Palynziq) is a genetically modified Phe ammonia lyase (PAL), an enzyme product of the cyanobacterium Anabaena variabilis that is PEGylated to decrease immunogenicity and increase half-life, as a novel treatment for PKU.

Pegvaliase is indicated for the treatment of patients with PKU aged ≥16 years who have inadequate blood Phe control (>600 µmol/l) despite prior management with available treatment options

Module SII: Non-clinical part of the safety specification

The non-clinical assessment of Kuvan supports the proposed recommended dose of Kuvan administered to patients with HPA due to PKU or BH4 deficiency. The Kuvan non-clinical program took into consideration the International Conference on Harmonisation (ICH) S6 guideline, "Preclinical Safety Evaluation of Biotechnology Derived Pharmaceuticals," CDER guidance "Nonclinical Safety Evaluation of Paediatric Drug Products" (February 2006), and BioMarin experience in development of similar enzyme replacement therapies treating lysosomal storage disorders. The non-clinical program consisted of in vitro primary pharmacodynamics, safety pharmacology, pharmacokinetics (PK), single- and repeat-dose toxicology, and developmental and reproductive toxicity studies evaluating Kuvan. Following is an overview of non-clinical studies conducted with Kuvan.

Key Safety Findings	Relevance to Human Usage
Toxicity	
Single- and repeat-dose toxicity Single-dose oral toxicology studies performed in mice, rats and marmoset monkeys showed sapropterin dihydrochloride has a low toxic potential with LD50s of 1400, 2300 and ≥1000 mg/kg, respectively. A chronic oral 52-week toxicity study was conducted in rats and marmoset monkeys to support the long-term treatment in patients. The most remarkable change seen after one year of daily dosing was the mild increase of slight histopathological basophilic changes in the renal collecting tubules of rats at the 400 mg/kg/day dose level. No kidney changes or other toxicities were observed in marmosets treated at 320 mg/kg/day for one year.	Kidney changes in rats are not considered serious since the histological alterations were slight, and there were no associated abnormal urinalysis or blood chemistry parameters. No kidney changes were seen in marmoset at doses and treatment duration comparable to those resulting in renal changes in rats. However, since the mechanism of the induced renal effects in rats is unknown, nephrotoxicity in humans is considered an important potential risk.

Key Safety Findings	Relevance to Human Usage
Reproductive and developmental toxicity Sapropterin dihydrochloride had no effect on fertility or implantation in rats. There was no developmental or embryofoetal toxicity observed in rats and rabbits. No adverse effects were detected in a pre- and post-natal toxicity study in rats as assessed through postnatal growth and developmental parameters of new-borns. Tissue distribution and milk excretion studies in pregnant and lactating rats indicated no foetal penetration or milk excretion after a single oral 10 mg/kg dose. However, the same dose administered intravenously resulted in some radioactive penetration in foetuses and increased excretion of total biopterin in milk. Such data indicate that foetal distribution of sapropterin dihydrochloride and excretion into the milk cannot be excluded.	There are limited data from use of Kuvan in pregnant women. Disease-associated maternal and/or embryo-foetal risk data from the Maternal Phenylketonuria Collaborative Study (MOMs) on 300-1,000 pregnancies and live births in PKU-affected women demonstrated that blood Phe higher than 600 µmol/L is associated with very high incidence of neurological, cardiac, facial dysmorphism, and growth anomalies. Therefore, not strictly controlling maternal blood Phe levels before and during pregnancy could be harmful to mother and foetus. Physician-supervised restriction of dietary Phe intake before and throughout pregnancy is the first choice of treatment in this patient group. The use of Kuvan should be considered only if strict dietary management does not adequately reduce blood Phe levels. Caution must be exercised when prescribing to pregnant women. It is not known whether sapropterin or its metabolites are excreted in human breast milk. Exercise caution when Kuvan is administered to a nursing woman.

Key Safety Findings	Relevance to Human Usage
Genotoxicity Sapropterin was noted to be positive in reverse mutation tests in *S. typhimurium* strains, TA98 at 625 or TA100 and TA1537 at 2500 mcg/plate. This finding was not supported by results of metabolic activation experiments. Sapropterin also produced chromosomal aberrations in Chinese hamster lung (CHL) and ovary (CHO) cells but was not mutagenic in cultured human lymphocytes from healthy donors (up to the concentration of 3200 mcg/mL) or when assessed in single (doses of up 2000 mg/kg) and multiple (2 or 4 daily doses of up 500 mg/kg) mouse oral micronucleus tests. Thus, while the *in vitro* mutagenicity tests were somewhat positive these results were neither confirmed by the chromosomal aberration test in human lymphocytes nor substantiated by the negative results in two *in vivo* tests for chromosomal damage using rodent (mouse) hematopoietic cells. The mutagenicity findings may be explained by auto-oxidation of sapropterin dihydrochloride producing reactive oxygen species, which, in turn, were responsible for the mutagenicity in bacteria and clastogenicity in transformed Chinese hamster cell lines. Negative results obtained in human peripheral lymphocyte cultures are thought to reflect their more efficient protective mechanisms as well as the high content of catalase from the co-cultured erythrocytes.	The negative results of in-vivo tests were consistent with expectations for a synthetic analogue of a natural cofactor. Overall, sapropterin dihydrochloride is considered without alerts for genotoxicity. In addition, a 10-year (March 1992 - March 2002) postmarketing surveillance study of sapropterin dihydrochloride (Biopten®) in treatment of BH4 deficiency enrolled 30 patients (27 diagnosed with BH4 deficiency and 3 diagnosed with PKU) and provided no evidence of genotoxic or mutagenic potential.
Carcinogenicity An increased frequency of benign adrenal tumours in treated male Fisher rats when compared to the concurrent vehicle control group has been observed in a 2-year oral carcinogenicity bioassay. However, the incidence is within the range of the testing facility historical control. Additionally, this finding was not confirmed in either female rats or in the mouse carcinogenicity bioassay.	Oral carcinogenicity studies conducted in mice and rats indicated no potential of Kuvan to induce the formation of either neoplastic or hyperplastic lesions. Additionally, since Kuvan is a synthetic formulation of the naturally occurring co-factor and the absence of hyperplastic/pre-neoplastic lesions in animals after chronic treatment, no significant carcinogenic risk to humans is expected from the therapeutic use of Kuvan.

General safety pharmacology	
Cardiovascular system There were no remarkable findings in oral safety pharmacology experiments conducted in rodents and dogs addressing the central nervous system, cardiovascular and respiratory functions. There were no effects on cardiovascular parameters including the QT interval in conscious dogs after single administration of up to 100 mg/kg sapropterin. Emesis was observed in dogs in relation to oral treatment with sapropterin dihydrochloride after an 18-hour fasting period. Such an effect was most likely due to the combination of the low pH of the formulation (pH range of 0.8 to 2.0) and prolonged fasting; emesis was detected after gavage with acidified vehicle but not observed when sapropterin dihydrochloride was administered orally to dogs in fed condition.	Emesis is related to the pH of the Kuvan solution and is potentially of relevance in clinical use. It is not considered to be a safety concern.

General safety pharmacology	
Mechanisms for drug-drug interactions	
Sapropterin dihydrochloride absorption from the gastrointestinal tract is limited and the fraction absorbed is mostly excreted with urine. Dedicated pharmacokinetic (PK) studies showed the absorption rate of sapropterin dihydrochloride through the gastro-intestinal tract was higher in young rats compared to adults with total Biopten levels in plasma or rats aged 4 days to 2 weeks at least one order of magnitude than that determined in rats aged 3 to 8 weeks. Repeated administration of sapropterin dihydrochloride to rats did not up-regulate Cytochrome P450-dependent drug-metabolizing enzymes in the liver microsomes. In vitro studies indicated sapropterin dihydrochloride does not induce or inhibit cytochrome P450 enzymes, including CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5, and it does not induce CYP 1A2, 2B6, or 3A4/5. DFHR inhibitors (eg, methotrexate, trimethoprim) may interfere with BH4 metabolism as the target enzyme is involved in the in vivo metabolism and recycling of sapropterin. Vasodilators acting through the nitric oxide (NO) system may get enhanced activity since BH4 is a cofactor for NO synthetase. Potential synergistic hypotensive effects may, therefore, occur with agents releasing NO or interfering with NO metabolism, including classical NO donors, phosphodiesterase type 5 inhibitors, and minoxidil. However, no interaction with sildenafil on cardiovascular effects in dogs or respiratory functions in rats was observed. Sapropterin dihydrochloride may increase the availability of tyrosine, a precursor to levodopa, hence, a drug interaction in patients receiving levodopa treatment may occur. Evidence from in-vitro data indicates potential for Kuvan to inhibit p-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) in the gut at therapeutic doses.	Although concomitant administration of inhibitors of dihydrofolate reductase (DFHR) (eg, methotrexate, trimethoprim) has not been studied, such medicinal products may interfere with BH4 metabolism. Caution is recommended when using such agents during treatment with Kuvan. BH4 is a cofactor for NO synthetase. Caution is recommended during concomitant use of Kuvan with all agents that cause vasodilation by affecting NO metabolism or action, including classical NO donors (eg, glyceryl trinitrate [GTN], isosorbide dinitrate [ISDN], sodium nitroprusside, molsidomine), phosphodiesterase type 5 inhibitors, and minoxidil. Caution should be exercised when prescribing Kuvan to patients receiving treatment with levodopa. Events of seizure, exacerbation of seizure, increased excitability and irritability have been observed during co-administration of levodopa and sapropterin in BH4-deficient patients. Findings from the clinical study (162-505) demonstrate that Kuvan does not affect the exposure to digoxin (and other P-gp substrates), and by extrapolation, it is unlikely affect BCRP substrates.

General safety pharmacology	
Other toxicity-related information or data Results of the acute studies conducted in juvenile mice and rats and of the 4-week toxicity study in juvenile rats were consistent with those obtained in similar studies conducted in adult animals, indicating that there are no age-related toxicities associated with sapropterin dihydrochloride administration. In preweaning rats, however, sapropterin dihydrochloride toxicity was shown at lower doses either in acute or in short-term repeat dose studies, with the kidney identified as the potential target organ of sapropterin dihydrochloride thus confirming that there were no undisclosed target organs of toxicity. Such a difference is most likely due to increased absorption rate of sapropterin dihydrochloride in the gastrointestinal tract of 2-weeks old animals and younger than an age-dependent sensitivity.	Kuvan is indicated for treatment of HPA in adult and paediatric patients with PKU or BH4 deficiency.

Conclusions of non-clinical data

Safety Concern	Conclusion
Important Identified Risks (confirmed by clinical data)	none
Important Potential Risks (not refuted by clinical data or which are of unknown significance)	**Nephrotoxicity:** Mild increase of slight histopathological changes in the kidney tubules of rats treated orally with 400 mg/kg/day Kuvan for one year. Increased frequency and degree of microscopic changes in kidneys of 7-day old rats (at study initiation) administered 320 mg/kg/day Kuvan for 2 weeks. **Drug interactions**: Based on the known pharmacology and metabolic pathways of Kuvan, interactions with DFHR inhibitors, vasodilators using the nitric oxide system and levodopa can be expected.
Missing information	none

Module SIII: Clinical trial exposure

Clinical trial exposure

Cumulative subject exposure from interventional clinical trials by BioMarin and Merck are presented below (Table SIII.1 and Table SIII.2). Overall cumulative subject exposure to Kuvan is based on actual exposure data from completed and ongoing interventional clinical trials. Clinical trial exposure is defined as having received at least one dose of Kuvan during a study. As of 01 December 2022 (DLP for the latest Periodic Benefit-Risk Evaluation Report [PBRER] #11), 1575 subjects have been exposed to Kuvan in interventional clinical trials sponsored by BioMarin or Merck. Cumulative exposure to Kuvan by demography of all ongoing and completed clinical trials by treatment duration (Table SIII.3), age group and sex (Table SIII.4), and racial group (Table SIII.5) are presented below. Exposure is also tabulated in special populations (Table SIII.6).

In BioMarin interventional clinical trials, 1276 subjects have been exposed to Kuvan: 182 healthy volunteers, 841 subjects with PKU or primary BH4 deficiency, and 253 subjects with diseases other than PKU or primary BH4 deficiency (hypertension, peripheral artery disease, or sickle cell disease). In Merck interventional clinical trials, 299 subjects have been exposed to Kuvan, amounting to 1575 subjects in total being exposed to Kuvan during interventional clinical trials.

Table SIII.1: Cumulative Subject Exposure in BioMarin Clinical Trials

Study	Phase	Type	Subjects
Studies in Healthy Volunteers			
PKU-005	1	Bioavailability	28
PKU-009	1	Bioavailability	44
PKU-013	1	Bioavailability	32
QTC-001	1	Cardiac signals	54
162-505	1	Drug-drug interaction	24
		Exposure in Volunteers	**182**
Studies in Subjects with PKU or BH4 Deficiency[a]			
PKU-001	2	Safety	488
PKU-003	3	Safety/Efficacy	NA (41)[a]
PKU-004	3	Safety/Efficacy	NA (80)[a]
PKU-006	3	Safety/Efficacy	87
PKU-007	2	Primary BH4 deficiency	12
PKU-008	3[a]	Safety/Efficacy	NA (111)[b]
PKU-015	3	Safety/Efficacy	95
PKU-016	3[a]	Safety/Efficacy	159
		Exposure in PKU or BH4 Deficiency	**841**
Studies in Subjects with Diseases other than PKU			
HTN-001	2	Hypertension	**77**
HTN-002	2	Hypertension	48
PAD-001	2	Peripheral artery disease	96
SCD-001	2	Sickle cell disease	32
		Exposure in diseases other than PKU	**253**
		TOTAL EXPOSURE	**1276**

BH4, tetrahydrobiopterin; NA, not applicable; PKU, phenylketonuria; NA, not applicable.

[a] Because PKU-003 and PKU-004 enrolled subjects from PKU-001, only PKU-001 exposure is considered to preclude double-counting.

[b] Because all PKU-008 enrolled subjects from PKU-006, only PKU-006 exposure is considered to preclude double-counting. In previous RMP version, it was reported that only 2 subjects treated previously with placebo in PKU-006 are counted (all other subjects were exposed in PKU-004 or PKU-006).

Table SIII.2: Exposure in Merck Clinical Trials

Study	Phase	Type (Age)	Subjects
Studies in Subjects with PKU			
162-502 (KOGNITO)	4	Neurocognition (4-5y)	48
162-503 (SPARK)[a]	3b	Safety/Efficacy/PK (<4y)	95
SIGNAL (700773-004)	2a	Neurocognition	7[b]
700773-510	3	Safety (4-18y)	90
ENDURE (700773-503)	2a	Neurocognition	59
	TOTAL EXPOSURE[c]		**299**

PK, pharmacokinetics.

[a] Prior to transfer of sponsorship from Merck to BioMarin (January 2016), study numbers were 700773-002 (KOGNITO) and 700773-003 (SPARK). SPARK exposure data provided by Merck to BioMarin prior to transfer of sponsorship included 45 subjects during BH4 testing, 19 subjects whose BH4 test was followed by Kuvan treatment, and 31 subjects who received Kuvan treatment without BH4 testing during the study.

[b] Study 700773-004 (SIGNAL), a Phase 2a neurocognition study in adults, which screened 10, enrolled 2, and exposed 7 subjects to Kuvan was closed prematurely due to poor recruitment.

[c] Eleven subjects rolled over from the SPARK study to the KOGNITO study; these subjects were counted twice in the overall totals.

Table SIII.3: Exposure by Duration

Duration (Months)	Number of Subjects	Subject-years
1 day to <1	881	14.4
1 to <6	332	89.98
6 to <12	39	21.5
12 to <24	65	100.23
24 to <36	56	136.5
36 to <48	0	0
48 to <60	1	5.0
60 to <72	6	33.9
72 to <84	54	370.56
84 to <96	33	232.54

Data for subject-years from Studies 162-505, 70073-510, 700773-004 (SIGNAL), and 700773-004 (ENDURE) were not available.

Data from Study 700773-003 (SPARK) are excluded, which were determined differently.

Table SIII.4: Exposure by Age Group and Sex

Age Group	Number of Subjects		
	Male	Female	Total
<1 year	15	20	35
1 to <2 years	19	22	41
2 to <4 years	41	44	85
4 to <7 years	59	64	123
4 to 16 years	14	13	27
>16 years	11	21	32
4 to 18 years	49	41	90
7 to <18 years	158	146	304
≥18 years	291	289	585

Study 700773-004 (SIGNAL) had 7 subjects but data on age was available only for 2 randomised subjects and data on sex was available only for 2 randomised subjects.

Grand totals reflect subjects counted once despite participation in more than one trial and age groups reflect subjects at the beginning of each trial. As such, subjects from PKU-003, PKU-004, and PKU-008 are not included in the grand totals to avoid double-counting. Note, 11 subjects rolled over from the SPARK study to the KOGNITO study; these subjects were counted twice in the overall totals.

Table SIII.5: Exposure by Racial Origin

Race	Number of Subjects
American Indian or Alaska native	6
Asian	18
Black or African American	29
Other	58
White	1147

Data for the Study 700773-503 (ENDURE) were not available.

[a] Study 700773-004 (SIGNAL) data on race of subjects only available for the 2 randomised subjects.

[b] Grand totals reflect subjects counted once despite participation in more than one trial except for 11 subjects who rolled over from the SPARK study to the KOGNITO study; these subjects were counted twice in the overall totals. As such, subjects from PKU-003, PKU-004, and PKU-008 are not included in the grand totals to avoid double-counting.

Table SIII.6: Exposure in Special Populations (All Clinical Studies)

Special Population	Subject	Subject-Year
Pregnant or lactating women	1	na
Lactating women	0	na
Unscreened/previously untreated adults	0	na
Paediatric subjects <4 years old	1	na
Hepatic or renal insufficiency	0	na

na=not applicable

Module SIV: Populations not studied in clinical trials

SIV.1: Exclusion criteria in pivotal clinical studies within the development programme

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Included as Missing Information? If No, Rationale.
Known hypersensitivity to active substance or excipient	Excluded as a precautionary measure in view of the safety risk.	No. As stated in SmPC Section 4.6, established hypersensitivity are a contraindication to Kuvan use.
Children <4 years old (8 years old in PKU-003, PKU-001, PKU-004)	Excluded for feasibility reasons: (a) uncontrolled HPA in subjects with PKU is more prevalent after early childhood, and (b) required stable diet challenging in this age group.	No. Literature reports no safety concern for the following groups: (a) >600 children with PKU <4 years old exposed to treatment with unregistered BH4 preparations, and (b) 35 children <4 years old received daily BH4 treatment for ≥2 months. In USA, Canada, and Australia, Kuvan is indicated in children <4 years old. CHMP adopted a Positive Opinion 21 May 2015 recommending authorisation of Kuvan Type II variation to extend indication to paediatric population <4 years old.
Pregnant, breast-feeding, or considering pregnancy	Because animal data indicate Kuvan penetration of fetus or excretion into human breast milk cannot be ruled out after high oral doses, pregnancy was an exclusion criterion in all Kuvan clinical trials.	Yes, for use in breast-feeding. Although there is no definitive justification to contraindicate Kuvan in pregnancy, strict diet should be tried first to control Phe levels; only if that fails should Kuvan be considered. As stated in SmPC Section 4.6, Kuvan should be used with caution in pregnancy, as amended following CHMP approval of Type II Variation on 18 December 2014, based on cases from KAMPER observational registry, the postmarketing safety database, and the literature.
Alanine aminotransferase >2 times Upper Limit of Normal	Excluded as precautionary measure	Yes. There were no hepatic concerns raised in non-clinical studies and no reports of hepatic abnormalities or treatment-related hepatic adverse events in the clinical development program. Hepatic laboratory shift tables, which addressed advice during the CHMP Protocol Assistance (EMEA/174572/2005), revealed no abnormalities. Accordingly, there is no safety reason to exclude these patients. However, SmPC Section 4.2 advises that Kuvan safety and efficacy in patients with hepatic insufficiency have not been

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Included as Missing Information? If No, Rationale.
		established. Caution must be exercised when prescribing to such patients.
Requirement for concomitant treatment with any drug known to inhibit folate synthesis (eg, methotrexate)	These drugs may interfere with BH4 metabolism and may have impacted efficacy and safety endpoints.	No. Whilst there is no definitive safety reason to contraindicate use of Kuvan in these patients, SmPC Section 4.5 provides a warning of potential for drug-drug interaction.
Concurrent use of levodopa	Concurrent levodopa use was an exclusion in studies PKU-001, PKU-004 and PKU-008 and based on very limited safety data from Study D272 (registration in Japan) in a subject with BH4 deficiency. Events of convulsion, exacerbation of convulsion, increased excitability and irritability have been observed during co-administration of levodopa and sapropterin in BH4-deficient patients.	No. Stated in SmPC Section 4.5, caution should be exercised when using Kuvan in patients concurrently using levodopa.
Concurrent disease potentially impacting safety assessment (eg, seizure Exclusion disorder, oral steroid-dependent asthma, or other condition requiring oral or parenteral corticosteroid administration, or insulin-dependent diabetes, history of organ transplantation). Serious neuropsychiatric illness (eg, major depression) not under medical control.	These were exclusion criteria for studies PKU-008 and PKU-007 as subjects with these conditions would have impacted the safety endpoints.	No. There is no safety justification to contraindicate Kuvan use in these patients.

SIV.2: Limitations to detect adverse reactions in clinical trial development programmes

Ability to Detect Adverse Drug Reactions (ADRs)	Limitation of Trial Programme	Implications for Target Population
That are common (≥1/100 to <1/10)	During the 12-month reporting period ending 01 December 2020 (inclusive), there were 101 serious and 1035 non-serious ADRs reported for Kuvan from spontaneous postmarketing sources.	ADRs with a frequency greater than 1 in 289 could be detected if there were no background incidence.
Due to prolonged exposure	The clinical trial programme has exposed up to 85 patients for 2 to<4 years.	No safety issue associated with duration of exposure up to 3 years has been identified. Because Kuvan mechanism of action and HPA require lifetime treatment, however, longer-term data are needed. Observational registries in US (PKUDOS) and EU (KAMPER) will study ≥500 patients to obtain data on prolonged exposure, cumulative effects, and long latency.

SIV.3: Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.1: Exposure of special populations included or not in clinical trial development programmes

Kuvan exposure in certain special patient populations is limited but open registries should contribute to the database and extend safety concerns.

Type of Special Population	Exposure
Pregnant women	Not included in clinical development program.
Breast-feeding women	Not included in clinical development program.
Elderly patients	Not included in clinical development program.
Population with relevant different ethnic origin	There was no restriction on the ethnicity or race of the subjects to be included in the clinical development programme.
Patients with relevant comorbidities	
Hepatically impaired patients	Not included in clinical development program.
Renally impaired patients	Not included in clinical development program.
BH4-deficient patients	Study PKU-007 studied safety and efficacy in this patient population. Twelve subjects (7 female, 5 male) were enrolled in the study, with the mean duration of exposure of 814.4 days.
Patients with moderate to severe neurocognitive disability	Not included in clinical development program.

Module SV: Post-authorisation experience

SV.1: Post-authorisation exposure

SV1.1: Method used to calculate exposure

Calculation of patient exposure is challenging because Kuvan dosage varies widely, depending on body weight and Phe level. The recommended dose is 10-20 mg/kg/day. Kuvan dispensing data were referenced to determine the mean daily dose for patients in North America. These data are received from specialty pharmacies daily. Because dispensing data are not available outside of North America, the mean daily dose was estimated using the North America dispensing data for those regions to be present a consistent exposure across all regions. The postmarketing exposure data are presented as number of patient-years.

Estimated patient exposure for all regions were calculated using a mean daily dose (in 100 mg equivalents) of 12.7 for tablet 100 mg, 3.5 for powder 100 mg, and 11.9 for powder 500 mg. This calculation of the patient-years was made to be consistent across all regions with the available data from North America.

SV1.2: Exposure

Cumulative patient exposure from marketing experience is estimated for patients exposed to Kuvan via commercial, compassionate, and named patient uses. Because registry patients use commercial product, Kuvan registry use is included here.

As of 01 December 2022, cumulative patient exposure to Kuvan (introduced in the US on 29 December 2007 and in the EU on 02 December 2008 [first marketing authorisation]) in the marketing setting was approximately 48,167 patient-years.

Included in this exposure estimation is cumulative exposure from US and European non-interventional observational registries is 2517 patients. In the PKUDOS registry, 1890 patients (and 53 pregnancies) have been registered from 68 sites in the US. In the KAMPER registry, 627 patients (and 26 pregnancies) have been registered from 69 sites in Europe (Table SV.1); 3 patients did not meet eligibility criteria and were not included in the safety analyses for the KAMPER final CSR.

As the generic product is available in the US since Q4 2020, the postmarketing surveillance data includes AE data from both the branded product, and for US only, the generic product.

Table SV.1: Post-authorization registry exposure for Kuvan

Registry	Population	Exposure (As of 31 May 2021)
KAMPER (Adult Maternal Paediatric European Registry)	all patients prescribed Kuvan (Europe)	627 patients 26 pregnancies Status: Completed
PKUDOS (PKU Demographics, Outcomes, and Safety Registry)	all patients prescribed Kuvan (US)	1890 patients 53 pregnancies Status: Completed

Module SVI: Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Kuvan has no known potential for drug abuse.

Module SVII: Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

As the initial approved version 1.3 (dated September 2008; generated by Merck) was not available, information generated from the RMP version 2.0 (dated 3 July 2009) is included. As per the RMP version 2.0 revision history, there is no change in the safety concerns from version 1.3. At the time of version 2.0 of the RMP (23 July 2009), the following safety concerns were identified:

Safety Concerns	
Important Identified Risks	Gastrointestinal disorders (Vomiting; Diarrhoea; Abdominal pain) Hypophenylalaninaemia (Blood Phe level < Lower Limit Normal) Rebound (Blood Phe level > 25% over Baseline) Drug interactions (Vasodilators using NO metabolism pathways; Inhibitors of dihydrofolate reductase; Levodopa)
Important Potential Risks	Nephrotoxicity
Missing Information	Size of safety database Limited long-term exposure data Limited BH4 deficiency subgroup data Subgroup experience: • Use in pregnancy and lactation • Use in children <4 years of age • Use in the elderly • Use in patients with hepatic failure • Use in patients with renal failure

SVII.1.1: Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risk	**Reason for Risk(s) not being Considered Important**
Headache Rhinorrhoea Pharyngolaryngeal pain Nasal congestion Cough	Risks with minimal clinical impact on patients (in relation to the severity of the indication treated).

SVII.1.2: Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk: Gastrointestinal disorders (Vomiting; Diarrhoea; Abdominal pain) Gastrointestinal disorders (Vomiting; Diarrhoea; Abdominal pain)

Risk-benefit impact:

Patients with HPA are not known to suffer from gastrointestinal disorders like vomiting, diarrhoea, or abdominal pain. These events were commonly observed in clinical studies with Kuvan. Though generally mild to moderate, risk of severe events leading to drug discontinuation is a risk.

Important Identified Risk: Hypophenylalaninaemia (Blood Phe level < Lower Limit Normal)

Risk-benefit impact:

Because of its pharmacological action, sapropterin may decrease blood Phe levels below the desired therapeutic level. Experience in clinical studies showed non-serious occurrences of hypophenylalaninemia, not resulting in clinically significant events. Cases are not likely to be severe as the nature of the disease and treatment is such that regular blood monitoring will take place. Thus, cases will be detected with blood Phe monitoring, and reversible with dose reduction. The potential for hypophenylalaninemia may indicate the need to modify the dosage or increase dietary Phe intake.

Important Identified Risk: Drug interactions (vasodilators using nitric oxide metabolism pathways; Inhibitors of DFHR; Levodopa)

Risk-benefit impact:

Potential synergistic effects with other medicinal products causing vasodilation, inhibiting DFHR or causing an increase of neurotransmitter may include hypotension, or increased excitability and irritability. Evidence for these interactions has largely come from literature reports and non-clinical studies; 1 subject with BH4 deficiency in a Japanese study had a possible interaction between Kuvan and levodopa. Studies for non PKU indications using another formation of sapropterin have shown a few patients who experienced convulsions, exacerbation of convulsions, over stimulation, or irritability during co-administration of levodopa and sapropterin.

Important Potential Risk: Nephrotoxicity

Risk-benefit impact:

An increased incidence of altered renal microscopic morphology (collecting tubule basophilia) was observed in rats following chronic oral administration of Sapropterin dihydrochloride at exposures at or slightly above the maximal recommended human dose. In clinical trials with sapropterin/Kuvan, in an open cohort study, it was reported that

4-aminotetrahydrobiopterin was associated with a risk of acute kidney injury at highest dose. No postmarketing reports of “nephrotoxicity” or “acute renal failure” have been received.

Missing Information: Size of safety database, Limited long-term exposure data, and Limited BH4 deficiency data

Risk-benefit impact:

The small size of target population, especially of BH4 subgroup, has limited our experience and therefore no inference to the presence or absence of subgroup specific safety issues can be made at this time. Experience will allow better characterisation of use and allow detection of unknown risks or verification of absence of risks.

Missing Information: Use in pregnancy and lactation

Risk-benefit impact:

The small size of target population has limited our experience and therefore no inference to the presence or absence of subgroup specific safety issues can be made at this time. Pregnant and lactation women were excluded from the clinical development programme. Experience in postmarketing setting and registry data will allow better characterisation of use; allow detection of unknown risks or verification of absence of risks.

Missing Information: Use in children <4 years of age

Risk-benefit impact:

The small size of target population has limited our experience and therefore no inference to the presence or absence of subgroup specific safety issues can be made at this time. Experience with drug usage in registries and clinical studies, and postmarketing setting will allow better characterisation of use.

Missing Information: Use in the elderly

Risk-benefit impact: The small size of target population has limited our experience and therefore no inference to the presence or absence of subgroup specific safety issues can be made at this time. Experience will allow better characterisation of use; allow detection of unknown risks or verification of absence of risks.

Missing Information: Use in patients with hepatic failure

Risk-benefit impact: An abnormal alanine aminotransferase (ALT) was an exclusion criterion in both placebo-controlled trials and in the largest open label trial in the development program. Therefore, experience with this subgroup is missing. Experience will allow better characterisation of use; allow detection of unknown risks or verification of absence of risks.

Missing Information: Use in patients with renal failure

Risk-benefit impact: In the pre-clinical program, nephrotoxicity was identified as a possible safety concern, based on studies in which very high doses of sapropterin were administered to animals. There were no subjects with renal insufficiency enrolled in clinical trials with Kuvan and therefore, the experience in this subgroup is missing. Experience will allow better characterisation of use; allow detection of unknown risks or verification of absence of risks.

SVII.2: New safety concerns and reclassification with a submission of an updated RMP

Table SVII.1: Major Changes to Categorisation of Safety Concerns in the Risk Management Plan over Time

RMP Version	Summary of Changes to Safety Concerns	Date of RMP
1.0	First Version	22 December 2006
1.1	• No changes to characterisation of the safety concerns in the RMP	05 May 2008
1.2	• Update Section 2.3. (actions proposed, inclusion of toxicological effect on kidneys as potential safety concern)	18 August 2008
1.3	• No changes to characterisation of the safety concerns in the RMP	18 September 2008
2.0	• No changes to characterisation of the safety concerns in the RMP	23 July 2009
3.0	• No changes to characterisation of the safety concerns in the RMP	25 January 2010
4.0	• Inclusion of respiratory disorders (rhinorrhoea, pharyngo-laryngeal pain, nasal congestion, and cough) as important identified risk upon request of TGA Australia • Inclusion of the following missing information: moderate to severe neurocognitive disability, history of seizures, psychiatric disorders upon request of TGA Australia	25 July 2010
5.0	• Update 1.5.1. Newly identified safety concerns • Inclusion of “convulsions” as potential risk into 1.5.2. (with subsequent changes in 1.10, 2.2., 2.3.,3.1, 5.)	24 January 2011
6.0	• Update 1.5.1. Newly identified safety concerns • Inclusion of “serious hypersensitivity reactions” and “epigastric ulcer” as important potential risk into Section 1.5.2. (with subsequent changes in 1.10, 2.2, 2.3, 3.1 and 5.)	16 January 2012
7.0	• Reclassification of potential risk “serious hypersensitivity reactions” to identified risk “hypersensitivity” Section 1.5.2. (with subsequent changes in Sections 1.10, 2.2, 2.3, 3.1 and 5.)	15 June 2012
8.0	• Removal of Identified risks of “Respiratory Disorders” “Gastrointestinal Disorders” and “Rebound” as these do not meet the definition of “Important” risks as per GVP Module V. • Addition of Potential risks: “Behavioural changes”, “Nephrolithiasis”, and Gastro-oesophageal reflux disease”, Removal of “patients with history of seizures or psychiatric	31 January 2014

RMP Version	Summary of Changes to Safety Concerns	Date of RMP
	disorders" from "missing information" as convulsions and behavioural disorders are now considered "potential risks"	
9.0	• No changes to characterisation of the safety concerns in the RMP	05 February 2015
10.0	• Removal of "Use of Kuvan in children 0-4 years old" as "missing information"	29 June 2016
11.0	• No changes to characterisation of the safety concerns in the RMP	31 January 2017
12.0	• Added information about powder dosage form of Kuvan	12 April 2017
13.0	• Gastritis added as an Identified Risk **Note: Change not accepted by the Agency**	14 July 2017
14.0	• No changes to characterisation of the safety concerns in the RMP **Note: Note: Agency commented on conversion to new template. Version not approved.**	12 July 2019
15.0	• No changes to characterisation of the safety concerns in the RMP • Agency comments addressed	04 October 2019
15.1	• Removal of the missing information size of safety database, long-term use, and limited BH4 deficiency data.	01 December 2021

15.2	• Removal of hypersensitivity; hypophenylalaninemia; and interaction with vasodilators using NO metabolism, DHFR, Inhibitors, or levodopa as an important identified risks
	• Removal of behavioural change, convulsion, including worsening; epigastric ulcer; gastrointestinal reflux disease; nephrotoxicity; nephrolithiasis; new-onset anxiety disorder; worsening psychiatric disorder as important potential risks
	• Retention of missing information regarding long-term use
	• Removal of 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
		06 May 2022

16.0	• Removal of the missing information long-term use	26 June 2023
16.1	• No changes to characterisation of the safety concerns in the RMP	8 November 2023
17.0	• No changes to characterisation of the safety concerns in the RMP	27 June 2024

SVII.2.1: Risk-benefit impact of new safety concerns added since the initial RMP

No new safety concerns associated with the use of Kuvan have been added to the RMP.

SVII.3: Details of important identified and potential risks from clinical development and post-authorisation experience (including newly identified)

SVII.3.1: Presentation of important identified risks and important potential risks

There are no important identified risks or important potential risks associated with the use of Kuvan.

SVII.3.2: Presentation of missing information

There are no areas of missing information associated with the use of Kuvan.

Module SVIII: Summary of the safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Important missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION STUDIES)

III.1: Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

None.

III.2: Additional pharmacovigilance activities

None.

III.3: Summary Table of Additional Pharmacovigilance Activities

Table III.1: On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable.				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Not applicable				

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMISATION MEASURES

Risk Minimisation Plan

There are no safety concerns associated with the use of Kuvan.

V.1: Routine Risk Minimisation Measures

No routine risk minimization activities are necessary.

V.2: Additional Risk Minimisation Measures

No additional risk minimisation activities are necessary.

V.3: Summary of Risk Minimisation Measures

No additional pharmacovigilance activities are necessary.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

Summary of Risk Management Plan for Kuvan (Sapropterin dihydrochloride)

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

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

This summary of the RMP for Kuvan 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 Kuvan's RMP.

I. The medicine and what it is used for

Kuvan is indicated for the treatment of hyperphenylalaninemia (HPA) in adults and paediatric patients of all ages with phenylketonuria (PKU) who have been shown to be responsive to such treatment. Kuvan is also indicated for the treatment of HPA in adults and paediatric patients of all ages with tetrahydrobiopterin (BH4) deficiency who have been shown to be responsive to such treatment. It contains sapropterin dihydrochloride as the active substance and it is given orally, as soluble tablets (100 mg) or as powder (100 or 500 mg), to be dissolved in water and drunk.

Further information about the evaluation of Kuvan's benefits can be found in Kuvan'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/kuvan

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

Important risks of Kuvan, together with measures to minimise such risks and the proposed studies for learning more about Kuvan's risks, 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 (eg, 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, including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Kuvan is not yet available, it is listed under 'missing information' below.

II.A. List of important risks and missing information

Important risks of Kuvan 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 Kuvan. 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 (eg, 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

There are no important identified or potential risks associated with the use of 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 Kuvan.

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

There are no other studies in the post-authorisation development plan.

PART VII: ANNEXES

Table of Contents

ANNEX 4: Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

ANNEX 6: Details of Proposed Additional Risk Minimisation Activities

Not applicable.

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Every: Approval Task	Susanna Heinonen Functional Representative (CW) EV QPPV 19-Jun-2024 19:05:54 GMT+0000

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