DATA SHEET KUVAN®
Sapropterin dihydrochloride
Soluble tablets (100 mg)

1. KUVAN® (100 mg soluble tablets)

KUVAN (sapropterin dihydrochloride) 100 mg soluble tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soluble tablet contains 100 mg of sapropterin dihydrochloride (equivalent to 77 mg of sapropterin).

Excipient(s) with known effect
Mannitol

For full list of excipients, see 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

Off-white to light yellow soluble tablets with "177" imprinted on one face.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

KUVAN is indicated for the treatment of hyperphenylalaninaemia (HPA) in sapropterin-responsive adult and paediatric patients with phenylketonuria (PKU) or tetrahydrobiopterin (BH4) deficiency (see 4.2 Dose and method of administration for definition of sapropterin responsiveness).

4.2. Dose and method of administration

Treatment with KUVAN must be initiated and supervised by a physician experienced in the treatment of PKU and BH4 deficiency.

KUVAN should be administered with a meal to increase 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.

For patients with BH4 deficiency, divide the total daily dose into 2 or 3 administrations, distributed over the day.

Active management of dietary phenylalanine and overall protein intake while taking KUVAN is required to ensure adequate control of blood phenylalanine levels and nutritional balance.

As HPA due to either PKU or BH4 deficiency is a chronic condition, once responsiveness is demonstrated, KUVAN is intended for long-term use.

Dose

PKU

The starting dose of KUVAN in adult and paediatric patients with PKU is 10 mg/kg body weight once daily. The dose is adjusted to achieve and maintain adequate blood phenylalanine levels as defined by the physician. The recommended daily dose is between 5 and 20 mg/kg/day.

BH4 deficiency

The starting dose of KUVAN in adult and paediatric patients with BH4 deficiency is 2 to 5 mg/kg body weight total daily dose. The dose is adjusted to achieve and maintain adequate blood phenylalanine levels as defined by the physician. The recommended total daily dose is between 2 and 20 mg/kg/day. Divide the total daily dose into 2 or 3 administrations, distributed over the day.

Determination of Response

Response to KUVAN cannot be accurately pre-determined by laboratory testing alone (e.g., molecular testing), and can only be determined by a therapeutic trial of KUVAN. Response to KUVAN is determined by a decrease in blood phenylalanine following treatment with KUVAN. A satisfactory response is defined as a ≥ 30 percent reduction in blood phenylalanine levels or attainment of the therapeutic blood phenylalanine goals defined for an individual patient by the treating physician.

Blood phenylalanine levels should be checked before initiating KUVAN and after 1 week of administration with KUVAN at the recommended starting dose. If an unsatisfactory reduction in blood phenylalanine levels is observed, then the dose of KUVAN can be increased weekly to a maximum of 20 mg/kg/day, with continued weekly monitoring of blood phenylalanine levels. Patients whose blood Phe does not decrease from baseline after 1 month of administration at 20 mg/kg per day are non-responders and these patients should not be treated with KUVAN and administration of KUVAN should be discontinued. The dietary phenylalanine intake should be maintained at a constant level during this period.

Once responsiveness to KUVAN has been established, the dose may be adjusted according to response to therapy within the therapeutic ranges specified under 'Dosage' above.

It is recommended that blood phenylalanine levels be tested one or two weeks after each dose adjustment and monitored frequently thereafter. Patients treated with KUVAN must continue a restricted phenylalanine diet and undergo regular clinical assessment (such as monitoring of blood phenylalanine, nutrient intake, and psycho-motor development).

Special Populations

Elderly Patients
The safety and efficacy of KUVAN in patients over 50 years of age, including adults who did not receive early dietary treatment, have not been established. Caution must be exercised when prescribing to elderly patients.

Renal and Hepatic Impairment
Safety and efficacy of KUVAN in patients with renal or hepatic insufficiency have not been established. Caution must be exercised when prescribing to patients with renal or hepatic insufficiency.

Method of Administration

The prescribed number of tablets should be placed in a glass or cup of water or apple juice and stirred until dissolved. It may take a few minutes for the tablets to dissolve. To make the tablets dissolve

faster they can be crushed. Small particles may be visible in the solution and will not affect the effectiveness of the medicinal product. The solution should be drunk within 15 to 20 minutes.

KUVAN tablets may also be crushed and then mixed in a small amount of soft foods such as yoghurt or mashed banana.

Patients above 20 kg body weight

KUVAN is provided as 100 mg tablets. The calculated daily dose based on body weight should be rounded to the nearest multiple of 100. For instance, a calculated dose of 401 to 450 mg should be rounded down to 400 mg corresponding to 4 tablets. A calculated dose of 451 mg to 499 mg should be rounded up to 500 mg corresponding to 5 tablets. The prescribed number of tablets should be placed in a glass or cup with 120 to 240 mL of water or apple juice and stirred until dissolved.

Children up to 20 kg body weight

The appropriate number of tablet(s) should be dissolved in a volume of water or apple juice depicted in Tables 1-4 based on the prescribed daily dose.

An accurate measuring device (e.g. medicine cup or oral dosing syringe) with suitable graduations should be used to ensure administration of the appropriate volume of solution. If only a portion of this solution needs to be administered, an oral dosing syringe should be used to withdraw the volume of solution to be administered. The solution may be transferred to another cup for administration of the medicine. For small infants who cannot drink from a cup, the solution corresponding to the prescribed daily dose may be administered into the mouth via the oral syringe. A 10 mL oral syringe should be used for administration of volumes of $\leqslant$10 mL and a 20 mL oral syringe for administration of volumes of >10 mL. Any unused portion should be discarded.

It is recommended that the prescriber, clinic nurse or pharmacist calculate and specify the volume of administration as well as the dose, in particular for young children, to reduce the risk of dosing errors.

Patients should be advised not to swallow the desiccant capsule found in the bottle of tablets.

Table 1: 2 mg/kg per day dosing table for children weighing up to 20 kg

Weight (kg)	Total dose (mg/day)	Number of tablets to be dissolved	Volume of dissolution (mL)	Volume of solution to be administered (mL)*
2	4	1	80	3
3	6	1	80	5
4	8	1	80	6
5	10	1	80	8
6	12	1	80	10
7	14	1	80	11
8	16	1	80	13
9	18	1	80	14
10	20	1	80	16
11	22	1	80	18
12	24	1	80	19
13	26	1	80	21
14	28	1	80	22
15	30	1	80	24
16	32	1	80	26
17	34	1	80	27
18	36	1	80	29
19	38	1	80	30
20	40	1	80	32

*Reflects volume for total daily dose.
Discard unused solution within 20 minutes.

Table 2: 5 mg/kg per day dosing table for children weighing up to 20 kg

Weight (kg)	Total dose (mg/day)	Number of tablets to be dissolved	Volume of dissolution (mL)	Volume of solution to be administered (mL)*
2	10	1	40	4
3	15	1	40	6
4	20	1	40	8
5	25	1	40	10
6	30	1	40	12
7	35	1	40	14
8	40	1	40	16
9	45	1	40	18
10	50	1	40	20
11	55	1	40	22
12	60	1	40	24
13	65	1	40	26
14	70	1	40	28
15	75	1	40	30
16	80	1	40	32
17	85	1	40	34
18	90	1	40	36
19	95	1	40	38
20	100	1	40	40

*Reflects volume for total daily dose.
Discard unused solution within 20 minutes.

Table 3: 10 mg/kg per day dosing table for children weighing up to 20 kg

Weight (kg)	Total dose (mg/day)	Number of tablets to be dissolved	Volume of dissolution (mL)	Volume of solution to be administered (mL)*
2	20	1	20	4
3	30	1	20	6
4	40	1	20	8
5	50	1	20	10
6	60	1	20	12
7	70	1	20	14
8	80	1	20	16
9	90	1	20	18
10	100	1	20	20
11	110	2	40	22
12	120	2	40	24
13	130	2	40	26
14	140	2	40	28
15	150	2	40	30
16	160	2	40	32
17	170	2	40	34
18	180	2	40	36
19	190	2	40	38
20	200	2	40	40

*Reflects volume for total daily dose.
Discard unused solution within 20 minutes.

Table 4: 20 mg/kg per day dosing table for children weighing up to 20 kg

Weight (kg)	Total dose (mg/day)	Number of tablets to be dissolved	Volume of dissolution (mL)	Volume of solution to be administered (mL)*
2	40	1	20	8
3	60	1	20	12
4	80	1	20	16
5	100	1	20	20
6	120	2	40	24
7	140	2	40	28
8	160	2	40	32
9	180	2	40	36
10	200	2	40	40
11	220	3	60	44
12	240	3	60	48
13	260	3	60	52
14	280	3	60	56
15	300	3	60	60
16	320	4	80	64
17	340	4	80	68
18	360	4	80	72
19	380	4	80	76
20	400	4	80	80

*Reflects volume for total daily dose.

Discard unused solution within 20 minutes.

Monitoring

Treatment with KUVAN may decrease blood phenylalanine levels below the desired therapeutic level. Adjustment of the KUVAN dose or modification of dietary phenylalanine intake may be required to achieve and maintain blood phenylalanine levels within the desired therapeutic range.

Blood phenylalanine and tyrosine levels should be tested, particularly in children, one to two weeks after each dose adjustment and monitored frequently thereafter, under the direction of the treating physician.

If inadequate control of blood phenylalanine 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 KUVAN.

Discontinuation of KUVAN treatment must be done only under the supervision of a physician due to the possibility of rebound in blood phenylalanine levels above pre-treatment levels (see 4.8 Undesirable effects). More frequent monitoring may be required, and dietary modification may be necessary to maintain blood phenylalanine levels within the desired therapeutic range.

4.3. Contraindications

KUVAN is contraindicated in patients with hypersensitivity to sapropterin or to any of the excipients (See 6.1 List of Excipients).

4.4. Special warnings and precautions for use

Specialist physician

Treatment with KUVAN should be directed by specialist physicians knowledgeable in the management of PKU and BH4 deficiency.

Determination of response

KUVAN does not work in all patients with PKU or BH4 deficiency but only in those who have shown a definite response. Response to treatment cannot be predetermined by laboratory testing (e.g. molecular testing) alone but can only be determined by a therapeutic trial of KUVAN (see 4.2 Dose and method of administration).

Dietary intake

Patients treated with KUVAN must continue a restricted phenylalanine diet and undergo regular clinical assessment (such as monitoring of blood phenylalanine and tyrosine levels, nutrient intake, and psycho-motor development).

Low blood phenylalanine levels

Sustained or recurrent dysfunction in the phenylalanine-tyrosine-dihydroxy-L-phenylalanine (DOPA) metabolic pathway can result in deficient body protein and neurotransmitter synthesis. Prolonged elevations in blood phenylalanine levels in patients with PKU and BH4 deficiency can result in severe neurologic damage, including severe mental retardation, microcephaly, delayed speech, seizures, and behavioural abnormalities. This may occur even if patients are taking KUVAN but not adequately controlling their blood phenylalanine levels within the recommended target range. Conversely, prolonged exposure to low blood phenylalanine and tyrosine levels during infancy has been associated

with impaired neurodevelopmental outcome. Active management of dietary phenylalanine and overall protein intake while taking KUVAN is required to ensure adequate control of blood phenylalanine and tyrosine levels and nutritional balance.

It is of primary importance to initiate KUVAN treatment as early as possible to avoid the appearance of non-reversible clinical manifestations of neurological disorders in paediatric patients and cognitive deficits and psychiatric disorders in adults due to sustained elevations of blood phenylalanine.

Convulsion disorders

Caution is advised when KUVAN is used in patients with predisposition to convulsions. Events of convulsion and exacerbation of convulsion have been reported in such patients.

KUVAN should be used with caution in patients who are receiving concomitant levodopa, as combined treatment may cause increased excitability and irritability. Events of convulsion and exacerbation of convulsion have been observed during co-administration of levodopa and sapropterin dihydrochloride in BH4-deficient patients (see section 4.5).

Intercurrent illness

Consultation with a physician is recommended during concomitant illness as blood phenylalanine levels may increase.

Gastritis and oesophagitis

Gastritis and oesophagitis were reported as serious adverse reactions. Monitor patients for signs and symptoms of these conditions.

Paediatric Population

The posology is the same in adults, children and adolescents.

Paediatric patients, aged 1 month and older, with HPA due to PKU and BH4 deficiency have been treated with KUVAN in clinical studies (see 5.1. Pharmacodynamic properties).

Published literature indicates that more than 2,700 children with PKU aged newborn to 4 years have been administered BH4, including at least 43 who received therapy for 2 months or longer. BH4 deficiency is an extremely rare condition but reports of published studies include at least 120 patients starting treatment when less than 4 years of age (see 5.1. Pharmacodynamic properties).

Carcinogenicity

In a 2-year rat oral carcinogenicity study there was a statistically significant increase in the incidence of benign adrenal phaeochromocytoma in male rats treated with 250 mg/kg/day sapropterin dihydrochloride (about 10 times human exposure based on AUC). No evidence of a carcinogenic effect was evident in an abbreviated 78-week oral carcinogenicity study in mice at sapropterin dihydrochloride doses up to 250 mg/kg/day (18 times human exposure based on AUC).

Genotoxicity

Sapropterin had variable mutagenic effects in bacterial cells and elicited an increase in chromosome aberrations in Chinese hamster lung and ovary cells. The results of the *in vitro* genotoxicity test in human lymphocytes were equivocal. Sapropterin has been shown to produce hydrogen peroxide in at

least one *in vitro* cell culture system, which may explain the positive results in these assays. Sapropterin was not genotoxic in *in vivo* mouse micronucleus tests.

4.5. Interactions with other medicines and other forms of interaction

In healthy subjects, administration of a single dose of KUVAN at the maximum therapeutic dose of 20 mg/kg had no effect on the pharmacokinetics of a single dose of digoxin (P-gp substrate) administered concomitantly.

Although concomitant administration of inhibitors of dihydrofolate reductase (e.g. 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 nitric oxide synthetase. Caution is recommended during concomitant use of KUVAN with all agents that cause vasodilation by affecting nitric oxide (NO) metabolism or action, including classical NO donors (e.g. glyceryl trinitrate (GTN), isosorbide dinitrate (ISDN), sodium nitroprusside (SNP), molsidomine), phosphodiesterase type 5 (PDE-5) inhibitors and minoxidil.

Caution should be exercised when prescribing KUVAN to patients receiving treatment with levodopa, as increased excitability and irritability has been reported during concomitant use. Events of convulsion and exacerbation of convulsion have been observed during co-administration of levodopa and sapropterin dihydrochloride in BH4-deficient patients.

4.6. Fertility, pregnancy and lactation

Pregnancy (Pregnancy Category B1)

There are limited data from the use of KUVAN in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development.

Available data from the Maternal Phenylketonuria Collaborative Study on 576 pregnancies and 414 live births in PKU-affected women demonstrated that uncontrolled phenylalanine levels above 600 µmol/L are associated with a very high incidence of neurological, cardiac, facial dysmorphism, and growth anomalies.

Maternal blood phenylalanine levels must be strictly controlled before and during pregnancy. If maternal phenylalanine levels are not strictly controlled before and during pregnancy, this could be harmful to the mother and the fetus. Physician-supervised restriction of dietary phenylalanine intake prior to and throughout pregnancy is the first choice of treatment in this patient group.

The use of KUVAN during pregnancy should be considered only if strict dietary management does not adequately reduce blood phenylalanine levels. Caution must be exercised when prescribing to pregnant women.

Breast-feeding

It is not known whether sapropterin or its metabolites are excreted in human breast milk. KUVAN should not be used during breastfeeding.

Fertility

Sapropterin dihydrochloride at oral doses up to 400 mg/kg/day (about 16 times the exposure in adults taking 20 mg/kg/day, based on AUC values) had no effect on the fertility of male or female rats.

4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8. Undesirable effects

Clinical Trials

In clinical trials, KUVAN has been administered to 579 patients with PKU in doses ranging from 5 to 20 mg/kg/day for lengths of treatment ranging from 1 week to 3 years. Patients were aged 4 to 48 years old at study entry. The patient population was nearly evenly distributed in gender, and approximately 95% of patients were Caucasian.

Approximately 35% of the 579 patients with PKU who received treatment with KUVAN in the clinical trials experienced adverse events. The overall incidence of adverse events in patients receiving KUVAN was similar to that reported with patients receiving placebo. The most commonly reported adverse reactions for which a causal relationship is at least a reasonable possibility are headache and rhinorrhoea.

Rebound, as defined by an increase in blood phenylalanine levels above pre-treatment levels, may occur upon cessation of treatment.

Table 5 shows by preferred term the number and percentage of 74 patients with PKU who had treatment-emergent adverse events (regardless of relationship) that occurred in at least 4% of patients following exposure to KUVAN at doses of 10 to 20 mg/kg/day for 6 to 10 weeks in 2 double-blind, placebo-controlled clinical trials.

Table 5: Treatment-emergent adverse events with an incidence ≥ 4% in patients following exposure to KUVAN in controlled clinical studies

System Organ Class	**Preferred Term**	**KUVAN** n=74 n (%)	**Placebo** n=59 n (%)
Any adverse event		47 (64)	42 (71)
Nervous system disorders	Headache	11 (15)	8 (14)
Infections and infestations	Upper respiratory tract infection[1]	9 (12)	14 (24)
Respiratory disorders	Rhinorrhoea	8 (11)	0
	Pharyngolaryngeal pain	7 (10)	1 (2)
	Cough	5 (7)	3 (5)
	Nasal congestion	3 (4)	0
Gastrointestinal disorders	Diarrhoea	6 (8)	3 (5)
	Vomiting	6 (8)	4 (7)
	Abdominal pain	4 (5)	5 (8)
General disorders and administration site conditions	Pyrexia[1]	5 (7)	4 (7)
Injury, poisoning and procedural complications	Contusion[1]	4 (5)	1 (2)
Skin and subcutaneous tissue disorders	Rash[1]	4 (5)	4 (7)

[1] Causal association with KUVAN is considered unlikely

In addition, hypophenylalaninaemia occurred in 2% patients treated with KUVAN (n=1) and in 12% patients treated with placebo (n=9).

In open-label, uncontrolled clinical trials in which all patients received KUVAN in doses of 5 to 20 mg/kg/day, adverse reactions were similar in type and frequency to those reported in the double-blind, placebo-controlled clinical trials.

In a clinical trial involving children who received treatment with sapropterin dihydrochloride, the most commonly reported adverse reactions are "amino acid level decreased" (hypophenylalaninemia), vomiting and rhinitis.

Post-marketing Experience

Cases of hypersensitivity reactions (including serious adverse reactions and rash), dyspepsia, gastritis, nausea, oesophageal pain, oropharyngeal pain, pharyngitis and oesophagitis have been observed in the post marketing setting.

A 10-year post-approval safety surveillance program of another formulation of the same active ingredient (sapropterin dihydrochloride granules) was conducted in Japan with 30 patients, 27 of these patients had BH4 deficiency and 3 had PKU. The most common adverse reactions identified during this program were convulsions and exacerbation of convulsions in 3 patients (see 4.4 Special warnings and precautions for use) and increased gamma-glutamyltransferase (GGT) in 2 patients.

Adverse events in New Zealand should be reported to the Centre for Adverse Reactions Monitoring (CARM) through their website https://nzphvc.otago.ac.nz or by calling (03) 479 7247.

4.9. Overdose

Headache and dizziness have been reported after the administration of KUVAN above the recommended maximum dose of 20 mg/kg/day. Treatment of overdose should be directed to symptoms. A shortening of the QT interval (-8.32 msec) was observed with a single supra-therapeutic dose of 100 mg/kg (5 times the maximum recommended dose).

Contact the Poisons Information Centre on 0800 POISON or 0800 764 766 for advice on management of overdosage.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products, Various alimentary tract and metabolism products, ATC code: A16AX07

Mechanism of Action

Hyperphenylalaninaemia (HPA) is diagnosed as an abnormal elevation in blood phenylalanine (Phe) levels and is usually caused by autosomal recessive mutations in the genes encoding for the liver enzyme phenylalanine hydroxylase (in the case of phenylketonuria, PKU) or for the enzymes involved in 6R-tetrahydrobiopterin (6R-BH4) biosynthesis or regeneration (in the case of BH4 deficiency). BH4 deficiency is a group of disorders arising from mutations or deletions in the genes encoding for one of the five enzymes involved in the biosynthesis or recycling of BH4.

In both PKU and BH4 deficiency, Phe cannot be effectively transformed into the amino acid tyrosine, leading to increased Phe levels in the blood. However, in patients with BH4 deficiency there are other enzymes in addition to phenylalanine hydroxylase that cannot function properly. These include tryptophan and tyrosine hydroxylase (located in the brain and other tissues) and nitric oxide synthase.

Sapropterin dihydrochloride is a synthetic version of the naturally occurring 6R-BH4, which is a cofactor of the hydroxylases for phenylalanine, tyrosine and tryptophan.

The rationale for administration of KUVAN in patients with BH4-responsive PKU is to enhance the activity of the defective phenylalanine hydroxylase and thereby increase or restore the oxidative metabolism of Phe sufficient to reduce or maintain blood Phe levels, prevent or decrease further Phe accumulation, and increase tolerance to Phe intake in the diet. The rationale for administration of KUVAN in patients with BH4 deficiency is to replace the deficient levels of BH4, thereby restoring the activity of phenylalanine hydroxylase.

In PKU patients who are responsive to BH4 treatment, blood Phe levels decrease within 24 hours after a single administration of KUVAN, although maximal effect on Phe level may take up to a month, depending on the patient. A single daily dose of KUVAN is adequate to maintain stable blood Phe levels over a 24-hour period. In a sub-study of the clinical trial described as 'Study 3' under Section 5.1 Pharmacodynamic Properties, Clinical Efficacy and Safety, blood Phe levels were measured multiple times over a 24-hour period in 12 patients taking 10 mg/kg/day. The blood Phe levels remained stable during the 24-hour observation period: mean (± Standard Deviation) was 661 (±433) μmol/L at pre-dose and 631 (±454) μmol/L at 24 hours post-dose; the lowest mean value during the 24-hour period was 477 (±241) μmol/L at 16 hours post-dose. No consistent relationship between meals and blood Phe levels was observed during the 24-hour period.

Clinical Efficacy and Safety

Phenylketonuria (PKU)

The efficacy and safety of KUVAN were evaluated in clinical trials in patients with PKU ranging in age from 1 month to 49 years old. Patients with significant concurrent diseases with potential to interfere with efficacy and safety analyses were excluded from the trials. The results of these studies demonstrate the efficacy of KUVAN to reduce blood Phe levels and to increase dietary Phe tolerance.

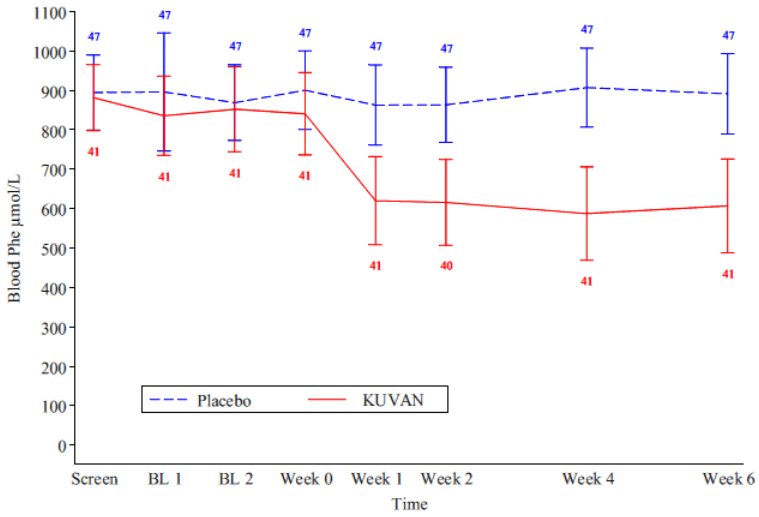
Study 1 was a multicentre, open-label, uncontrolled clinical trial of 489 patients with PKU who had baseline blood Phe levels ≥ 450 μmol/L. Patients ranged in age from 8 to 48 years (38 patients were 8-11 years old and 451 were 12 years of age or older). Patients were to receive treatment with KUVAN 10 mg/kg/day for 8 days. For the purposes of this study, response to KUVAN treatment was defined as a ≥ 30% decrease in blood Phe from baseline. At Day 8, 96 patients (20%) were identified as responders.

Study 2 was a multicentre, double-blind, placebo-controlled trial of patients with PKU who responded to KUVAN in Study 1. After a washout period from Study 1, patients were randomised equally for 6 weeks of treatment with KUVAN 10 mg/kg/day or placebo. Four (10%) of the 41 KUVAN-treated patients and 8 (17%) of the 47 placebo patients were 8-11 years old; all other treated patients were 12 years of age or older. Efficacy was assessed by the mean change in blood Phe level from baseline to Week 6 in the KUVAN–treated group as compared to the mean change in the placebo group.

The results showed that KUVAN 10 mg/kg/day significantly reduced blood Phe levels as compared to placebo (See Figure 1). The baseline blood Phe levels for the KUVAN-treated group and the placebo group were similar, with mean (±SD) baseline blood Phe levels of 843 (±300) μmol/L and 888 (±323) μmol/L, respectively. The mean (±SD) decrease from baseline in blood Phe levels at the end of the 6 week study period was 236 (±257) μmol/L for the KUVAN treated group as compared to an increase of 3 (±240) μmol/L for the placebo group ($p<0.001$). For patients with baseline blood Phe levels ≥ 600

µmol/L, 42% (13/31) of those treated with KUVAN and 13% (5/38) of those treated with placebo had blood Phe levels < 600 µmol/L at the end of the 6-week study period (p=0.012).

Figure 1: Mean Blood Phe Levels over 6 Weeks (LOCF)



Displayed are mean blood Phe values for each treatment group at each visit and the associated 95% CIs. The numbers above and below the lines are the number of subjects who have data at a given time-point. BL refers to Baseline Visit.

Study 3 was a multicentre, open-label, 22-week extension study in which 80 patients who responded to treatment in Study 1 and completed Study 2 were treated. During the first 6 weeks of Study 3, patients underwent forced dose-titration with 3 different doses of KUVAN. Treatment during this dose titration period consisted of 3 consecutive 2-week courses of KUVAN at doses of 5, then 20, and then 10 mg/kg/day. At baseline, mean (±SD) blood Phe was 844 (±398) µmol/L. At the end of treatment with 5, 10, and 20 mg/kg/day, mean (±SD) blood Phe levels were 744 (±384) µmol/L, 640 (±382) µmol/L, and 581 (±399) µmol/L, respectively.

During the period from Week 6 to Week 10, patients were maintained on KUVAN 10 mg/kg/day pending analysis of their blood Phe results from the forced-dose titration period. Starting at the Week 10 visit, each patient was assigned to receive a fixed dose of 5, 10 or 20 mg/kg/day based on their blood Phe results measured at the Week 2 and Week 6 visit, then continued using this optimal KUVAN dose until the Week 22 visit. Of the 80 patients, 6 (8%) received 5 mg/kg/day, 37 (46%) received 10 mg/kg/day and 37 (46%) received 20 mg/kg/day KUVAN from Week 10 to Week 22. Patients who received 10 or 20 mg/kg/day at all time points between Week 10 and Week 22 had mean blood Phe levels during this time comparable to those obtained on the same dose during the forced dose-titration period. Patients treated with 5 mg/kg/day from Week 10 to Week 22 had mean blood Phe levels higher than during the forced dose-titration period.

The mean (±SD) blood Phe levels at the Weeks 12-22 visits ranged between 620 (±371) and 652 (±383) µmol/L. On average, patients maintained a stable reduction in Phe levels. The 95% confidence interval for the mean change from baseline blood Phe level at the first visit after subjects started using their optimal dose was (-297 µmol/L, -152 µmol/L), and each of the 95% confidence intervals for the mean change from baseline blood Phe level at Weeks 16, 20 and 22 overlap with this interval indicating persistence of the effect of KUVAN treatment.

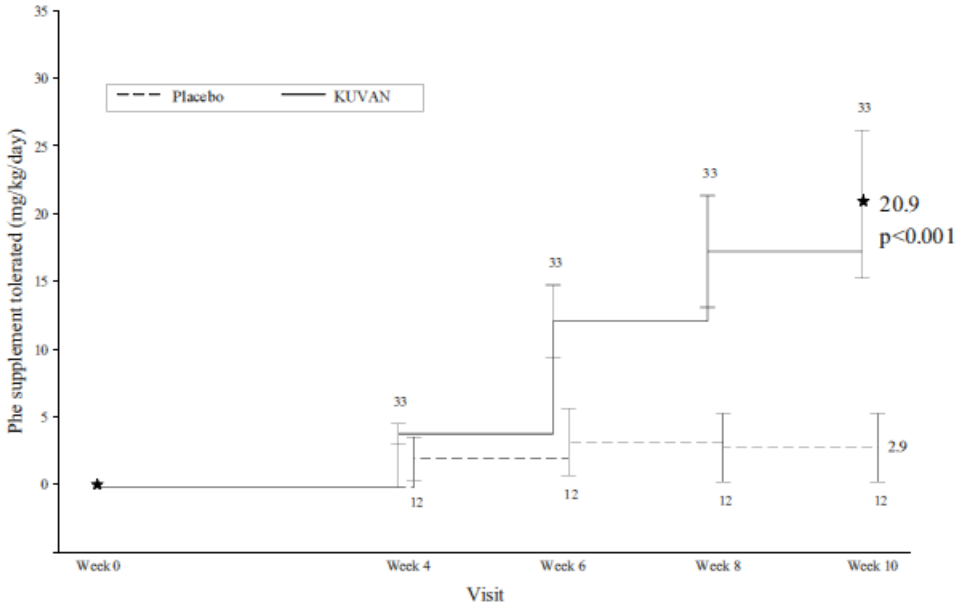
Study 4 was a two-part, phase III study in PKU patients who were following a strict Phe restricted diet and who had blood Phe levels of ≤ 480 µmol/L at screening. In the first part of the study, there were 90 patients ranging in age from 4 to 12 years old inclusive; 50 (56%) were 4-7 years old, 37 (41%) were 8-11 years old and the remaining 3 (3%) were 12 years old. All patients (n=90) were treated with open-label KUVAN 20 mg/kg/day for 8 days. Response to KUVAN was defined as a ≥ 30% decrease

in blood Phe from baseline and blood Phe ≤ 300 µmol/L at Day 8. At Day 8, 50 patients (56%) had a ≥ 30% decrease in blood Phe and blood Phe level ≤ 300 µmol/L on Day 8 and were therefore eligible to enrol in the second part of the study.

The second part of Study 4 was a randomised, double-blind, placebo-controlled trial in which subjects were randomised 3:1 to treatment with KUVAN 20 mg/kg/day (n=34) or placebo (n=12) for 10 weeks. Of the 33 patients who received at least one dose of KUVAN, 16 (48.5%) were 4-7 years old, 15 (45.5%) were 8-11 years old and the remaining 2 (6.0%) were 12 years old. After 3 weeks of treatment with KUVAN 20 mg/kg/day, blood Phe levels were significantly reduced; the mean (±SD) decrease from baseline in blood Phe level within this group was 149 (±134) µmol/L (p<0.001). After 3 weeks, subjects in both the KUVAN and placebo treatment groups were continued on their Phe-restricted diets and dietary Phe intake was increased or decreased using standardised Phe supplements with a goal to maintain blood Phe levels at < 360 µmol/L. The mean (±SD) increase in dietary Phe tolerance was 17.5 (±13.3) mg/kg/day for the KUVAN group compared to 3.3 (±5.3) mg/kg/day for the placebo group (p=0.006). For the KUVAN treatment group, the mean (±SD) total dietary Phe tolerance was 38.4 (±21.6) mg/kg/day during treatment with KUVAN compared to 15.7 (±7.2) mg/kg/day before treatment.

The Week 10 mean (±SD) Phe supplement tolerated by subjects treated with KUVAN was 20.9 (±15.4) mg/kg/day, a value that was significantly increased (p<0.001) from the pre-treatment value of zero, versus 2.9 (±4.0) mg/kg/day in the placebo group (p=0.027, statistically significant increase from zero but not clinically meaningful) (See Figure 2).

Figure 2: Phe Supplement Tolerated by Treatment Arm



The graph presents Phe supplement tolerated and the 95% confidence intervals at Weeks 4, 6, 8, and 10.
The numbers at each visit are the number of subjects in each mean calculation.
The primary efficacy analysis compared the values indicated by a star, using a one-sample t-test.

Subjects from Study 3 and the second part of Study 4 were eligible to enter a phase IIIb multicentre, open-label extension study to evaluate the safety of long-term treatment up to 3 years. Although the study was not designed to evaluate efficacy, it was notable that overall blood Phe concentrations remained less than 600 µmol/L.

Paediatric population

The safety, efficacy and population pharmacokinetics of sapropterin dihydrochloride in paediatric patients aged <7 years were studied in two open-label studies.

The first study (Study 5) was a multicentre open-label randomised controlled study in children <4 years old with a confirmed diagnosis of PKU.

56 paediatric PKU patients <4 years of age were randomised 1:1 to receive either 10 mg/kg/day sapropterin dihydrochloride plus a phenylalanine-restricted diet (n=27), or just a phenylalanine-restricted diet (n=29) over a 26-week Study Period.

It was intended that all patients maintained blood phenylalanine levels within a range of 120-360 µmol/L (defined as ≥120 to <360 µmol/L) through monitored dietary intake during the 26-week Study Period. If after approximately 4 weeks, a patient's phenylalanine tolerance had not increased by >20% versus baseline, the sapropterin dihydrochloride dose was increased in a single step to 20 mg/kg/day.

The results of Study 5 demonstrated that daily dosing with 10 or 20 mg/kg/day of sapropterin dihydrochloride plus phenylalanine-restricted diet led to statistically significant improvements in dietary phenylalanine tolerance compared with dietary phenylalanine restriction alone while maintaining blood phenylalanine levels within the target range (≥ 120 to < 360 µmol/L). The adjusted mean dietary phenylalanine tolerance in the sapropterin dihydrochloride plus phenylalanine-restricted group was 80.6 mg/kg/day and was statistically significantly greater ($p < 0.001$) than the adjusted mean dietary phenylalanine tolerance in dietary phenylalanine therapy alone group (50.1 mg/kg/day). In the clinical trial extension period, patients maintained dietary phenylalanine tolerance while on KUVAN treatment in conjunction with a Phe restricted diet, demonstrating sustained benefit over 3.5 years.
The second study (Study 6) was a multicentre, uncontrolled, open-label study designed to evaluate the safety and effect on preservation of neurocognitive function of KUVAN 20 mg/kg/day in combination with a phenylalanine-restricted diet in children with PKU less than 7 years of age at study entry. Part 1 of the study (4 weeks) assessed patients' response to KUVAN; Part 2 of the study (up to 7 years of follow-up) evaluated neurocognitive function with age-appropriate measures and monitored long-term safety in patients responsive to KUVAN. Patients with pre-existing neurocognitive impairment (IQ <80) were excluded from the study. Ninety-five patients were enrolled into Part 1, and 65 patients were enrolled into Part 2, of whom 49 (75%) patients completed the study with 27 (42%) patients providing Full Scale IQ (FSIQ) data at year 7.

Mean Indices of Dietary Control were maintained between 133 µmol/L and 375 µmol/L blood phenylalanine for all age groups at all time points. At baseline, mean Bayley-III score (102, SD=9.1, n=26), WPPSI-III score (98.8-100.4, SD=14.0-15.4, n=59) and WISC-IV score (113, SD=9.8, n=4) were within the average range for the normative population.

Among 62 patients with a minimum of two FSIQ assessments, the 95% lower limit confidence interval of the mean change over an average 2-year period was -1.6 points, within the clinically expected variation of ±5 points. No additional adverse reactions were identified with long-term use of KUVAN for a mean duration of 6.5 years in children less than 7 years of age at study entry.

BH4 Deficiency

Evidence of the safety and effectiveness of KUVAN for the treatment of HPA due to BH4 deficiency is provided by the results of analysis of data from a study conducted with KUVAN, results from studies conducted with sapropterin dihydrochloride granules registered in Japan for this indication, and published studies of clinical experience with BH4 identified via a systematic literature review. Clinical experience reported in published literature includes prospective and retrospective open-label studies, using both Phe blood levels and clinical outcomes (e.g. IQ and development measures), to determine efficacy. Approximately 120 patients were less than 4 years old at start of treatment, including 104 who started treatment when less than 1 year old.

An open-label, multicentre clinical trial evaluating the efficacy and safety of KUVAN for the treatment of HPA due to BH4 deficiency enrolled 12 patients, 9 with defects in enzymes of BH4 biosynthesis and 3 with defects in enzymes involved in BH4 recycling. Patients ranged in age from 3 to 35 years, 1 (8%) less than 4 years, 3 (25%) between 4-7 years, 2 (17%) between 8-11 years, and the remaining 6 patients (50%) were 12 years of age or older. Patients receiving an unregistered formulation of BH4 prior to study entry started treatment with KUVAN at approximately the same daily dose as the prior BH4 dose; other patients commenced treatment at 5 mg/kg/day. Dose adjustment up or down to a maximum of 20 mg/kg/day was permitted at study Week 6. Mean (±SD) blood Phe remained at levels similar to baseline (133 ± 135 μmol/L) at all study visits during treatment with KUVAN. Most subjects remained below the blood Phe target of < 360 μmol/L at all study visits, including all patients with defects in enzymes of BH4 biosynthesis.

A study with sapropterin dihydrochloride 2.5% granules was conducted in 16 patients with BH4 deficiency treated with 2-5 mg/kg/day for a mean of 15.5 months. Blood Phe levels were reduced by sapropterin dihydrochloride, and were maintained within normal range for the duration of treatment. Based on a rating of global improvement, there was moderate or marked improvement in all 16 subjects. Subjects from this study together with another 14 subjects were subsequently entered into a post-marketing surveillance study. Although patients were meant to have BH4 deficiency, 3 were subsequently found to have HPA due to PKU. All 30 patients were treated for at least one year, with 19 patients treated for 10-20 years. For the study population with BH4 deficiency, 25/27 (93%) achieved a global improvement rating of 'markedly improved', 'improved' or 'slightly improved'.

5.2. Pharmacokinetic properties

Absorption

Sapropterin is absorbed after oral administration of the dissolved tablet and the maximum blood concentration (C_{max}) is achieved 3 to 4 hours after dosing in the fasted state. The rate and extent of absorption of sapropterin is influenced by food. Compared to fasting, absorption is higher after a high-fat, high-calorie meal, resulting, on average, in 40-85% higher maximum blood concentrations achieved 4 to 5 hours after administration. Neither the absolute bioavailability nor the bioavailability after oral administration in humans is known.

Distribution

In non-clinical studies, sapropterin was primarily distributed to the kidneys, liver, adrenal glands and spleen as assessed by levels of total and reduced biopterin concentrations (see also 4.6 Fertility, pregnancy and lactation, Breast-feeding and 4.4 Special warnings and precautions for use, Paediatric Population).

In rats, following intravenous administration of radiolabelled sapropterin, radioactivity was found to be distributed in fetuses. No increase in total biopterin concentrations in fetuses was observed in rats after oral administration of 10 mg/kg sapropterin dihydrochloride. Very small amounts of sapropterin were distributed to the brain in adult rats but in juvenile rats, total brain biopterin levels were significantly increased following sapropterin administration.

However, in pregnant guinea pigs there was a marked increase in sapropterin and/or its metabolites in the fetus after oral administration of 20 mg/kg sapropterin dihydrochloride.

Biotransformation

6R-BH4 is primarily metabolised in the liver with dihydrobiopterin and dihydroxanthopterin as the main human metabolites. Since sapropterin is a synthetic version of the naturally occurring 6R-BH4, it

can be reasonably anticipated to undergo the same metabolism, including 6R-BH4 regeneration. Folic acid and vitamin B12 may increase BH4 levels.

Elimination

The mean elimination half-life of KUVAN in PKU patients was approximately 6-7 hours. Following intravenous administration in rats, sapropterin is mainly excreted in the urine. Following oral administration it is mainly excreted in the faeces while a small proportion is excreted in urine.

Population pharmacokinetics

Population pharmacokinetic analysis of sapropterin including patients from birth to 49 years of age showed that body weight is the only covariate substantially affecting clearance or volume of distribution

5.3. Preclinical Safety Data

No clear evidence of teratogenic activity was found in rats or rabbits at doses of 400 and 600 mg/kg/day, corresponding to about 16 and 19 times, respectively, the exposure in adults at the maximum recommended human dose (based on AUC). Sapropterin dihydrochloride had no effect on parturition and postnatal development in rats at doses of 400 mg/kg/day

Excretion of total biopterin in milk occurred in rats when sapropterin dihydrochloride (10 mg/kg) was administered by the intravenous route. No increase in total biopterin concentrations in milk was observed in rats after oral administration of 10 mg/kg sapropterin dihydrochloride. There were no effects on the development of rat pups of dams given 400 mg/kg/day sapropterin dihydrochloride orally from gestation Day 17 to post-partum Day 20 (approximately 16 times the exposure in adults at the maximum recommended human dose, based on AUC).

An increased incidence of altered renal microscopic morphology (collecting tubule basophilia) was observed in rats following chronic oral administration of sapropterin dihydrochloride at doses higher than 80 mg/kg/day, i.e. at exposures (based on area under curve, AUC) about 3 times the exposure at the maximal recommended human dose. No kidney changes were seen in marmoset monkeys after chronic treatment at oral doses of up to 320 mg/kg/day, approximately 2.6-times the highest dose anticipated in humans, based on body surface area.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Mannitol
Calcium hydrogen phosphate
Crospovidone
Ascorbic acid
Sodium stearyl fumarate
Riboflavin

6.2. Incompatibilities

Not applicable

6.3. Shelf life

3 years

6.4. Special precautions for storage

Store below 25°C.
Keep the bottle tightly closed in order to protect from moisture.
Product should be used within two months after first opening the bottle.

6.5. Nature and contents of container

High-density polyethylene (HDPE) bottles with child-resistant closure. The bottles are sealed with an aluminium seal. Each bottle contains a small plastic tube of desiccant (silica gel). Each bottle is packaged in an individual carton and contains 30, 120 or 240[#] tablets.

[#]Not all pack sizes are being distributed in New Zealand.

6.6. Special precautions for disposal and other handling

No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Pharmacy Retailing (NZ) Limited t/a Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks 2022
Auckland

For enquiries about KUVAN, contact medinfoasia@bmrn.com or call BioMarin on 0800 882 012.
To report adverse events, contact drugsafety@bmrn.com or call BioMarin on 0800 882 012.

9. DATE OF FIRST APPROVAL

12 May 2011

10. DATE OF REVISION OF THE TEXT

15 July 2021

Summary table of changes

Section changes	Summary of new information
4.2, 4.4	Deletion of statements indicating that there are limited data on the long-term use of Kuvan
5.1	Addition of data from the PKU-015 paediatric clinical study
10	Company contact details updated

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