Prescribing Information

KUVAN®

1. NAME OF THE MEDICINAL PRODUCT

Kuvan® 100 mg soluble tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kuvan is indicated for the treatment of hyperphenylalaninaemia (HPA) in adults and paediatric patients of all ages with phenylketonuria (PKU) who have been shown to be responsive to such treatment (see section 4.2).

Kuvan is also indicated for the treatment of hyperphenylalaninaemia (HPA) in adults and paediatric patients of all ages with tetrahydrobiopterin (BH4) deficiency who have been shown to be responsive to such treatment (see section 4.2).

4.2 Posology and method of administration

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

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. However, there are limited data regarding the long-term use of Kuvan.

Posology

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.

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, usually between 5 and 20 mg/kg/day, to achieve and maintain adequate blood phenylalanine levels as defined by the physician.

BH4 deficiency

The starting dose of Kuvan in adult and paediatric patients with BH4 deficiency is 2 to 5 mg/kg body weight total daily dose. Doses may be adjusted up to 20 mg/kg per day.

Paediatric population

The posology is the same in adults and children.

Elderly patients

Safety and efficacy of Kuvan in patients above 65 years of age have not been established. Caution must be exercised when prescribing to elderly patients.

Patients with renal or 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 such patients.

Determination of Response

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.

Response to Kuvan is determined by a decrease in blood phenylalanine following treatment with Kuvan. Blood phenylalanine levels should be checked before initiating Kuvan and after 1 week of treatment 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 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 phenylalanine 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 of administration of Kuvan 20 mg/kg/day should be considered non-responsive and should not receive treatment with Kuvan.

Once responsiveness to Kuvan has been established, the dose may be adjusted within the range of 5 to 20 mg/kg/day according to response to therapy.

It is recommended that blood phenylalanine and tyrosine levels be tested one or two weeks after each dose adjustment and monitored frequently thereafter under the direction of the

treating physician. 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).

Dose adjustment

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 should be done only under the supervision of a physician. More frequent monitoring may be required, as blood phenylalanine levels may increase. Dietary modification may be necessary to maintain blood phenylalanine levels within the desired therapeutic range.

Method of administration

Kuvan tablets 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.

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

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

The prescribed number of tablets should be placed in a glass or cup of water 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 drank within 15 to 20 minutes.

Adults

The prescribed number of tablets should be placed in a glass or cup with 120 to 240 ml of water and stirred until dissolved.

Paediatric population

Children above 20 kg body weight
The prescribed number of tablets should be placed in a glass or cup with up to 120 ml of water and stirred until dissolved.

Children up to 20 kg body weight
The devices required for dosing in children up to 20 kg body weight (i.e. medicine cup with graduations at 20, 40, 60, 80 ml; 10 ml and 20 ml oral dosing syringes with graduation at 1 ml divisions) are not included in the Kuvan pack. These devices are supplied to the

specialized paediatric centers for inborn errors of metabolism to be provided to the caregivers of the patients.

Depending on the dose (in mg/kg/day) the appropriate number of tablets should be dissolved in a volume of water as depicted in Tables 1-4, whereby the volume of the solution to be administered is calculated according to the prescribed daily dose. The prescribed number of tablets for a 2, 5, 10 and 20 mg/kg/day dose should be placed in a medicine cup (that shows the appropriate graduation markings at 20, 40, 60 and 80 ml) with the amount of water as depicted in Tables 1-4 and stirred until dissolved.

If according to the prescribed daily dose 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 from the medicine cup and transferred to a glass or a cup for administration of the medicine. For small infants who cannot drink from a glass or a cup the solution corresponding to the prescribed daily dose may be administered into the mouth via the oral dosing syringe. A 10 ml oral dosing syringe should be used for administration of volumes of ≤ 10 ml and a 20 ml oral dosing syringe for administration of volumes of > 10 ml.

Table 1 provides dosing information for children up to 20 kg at a dose of 2 mg/kg per day, Table 2 for dosing information at 5 mg/kg per day, Table 3 for dosing information at 10 mg/kg per day and Table 4 for dosing information at 20 mg/kg per day.

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 for tablet solution.

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 for tablet solution

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 for tablet solution

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 for tablet solution

After administration: Throw away any remaining solution as it should not be used beyond 20 minutes.

For cleaning, remove the plunger from the barrel of the oral dosing syringe. Wash both parts of the oral dosing syringe and the medicine cup with warm water and air dry. When the oral dosing syringe is dry, put the plunger back into the barrel. Store the oral dosing syringe and the medicine cup for next use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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 and tyrosine 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 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.

Health disturbances

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

Convulsions disorders

Caution should be exercised when prescribing Kuvan to patients receiving treatment with levodopa. Cases of convulsion, exacerbation of convulsion, increased excitability and irritability have been observed during co-administration of levodopa and sapropterin in BH4-deficient patients (see section 4.5).

Discontinuation of treatment

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

There are limited data regarding the long-term use of Kuvan.

Sodium content

This medicine contains less than 1 mmol (23 mg) sodium per tablet, i.e. essentially “Sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

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 medicinal products while taking Kuvan.

BH4 is a cofactor for nitric oxide synthetase. Caution is recommended during concomitant use of Kuvan with all medicinal products that cause vasodilation, including those administered topically, by affecting nitric oxide (NO) metabolism or action including classical NO donors (e.g. glyceryl trinitrate (GTN), isosorbide dinitrate (ISDN), sodium nitroprusside (SNP), molsidomin), phosphodiesterase type 5 (PDE-5) inhibitors and minoxidil.

Caution should be exercised when prescribing Kuvan to patients receiving treatment with levodopa. Cases of convulsion, exacerbation of convulsion, increased excitability and irritability have been observed during co-administration of levodopa and sapropterin in BH4-deficient patients.

4.6 Fertility, pregnancy and lactation

<u>Pregnancy</u>

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

Available disease-associated maternal and/or embryofoetal risk data from the Maternal Phenylketonuria Collaborative Study on a moderate amount of pregnancies and live births (between 300-1,000) 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 therefore 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 foetus. 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 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 breast-feeding.

Fertility

In preclinical studies, no effects of sapropterin on male and female fertility were observed.

4.7 Effects on ability to drive and use machines

Kuvan has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Approximately 35% of the 579 patients aged 4 years and over who received treatment with sapropterin dihydrochloride (5 to 20 mg/kg/day) in the clinical trials for Kuvan experienced adverse reactions. The most commonly reported adverse reactions are headache and rhinorrhoea.
In a further clinical trial, approximately 30% of the 27 children aged below 4 years who received treatment with sapropterin dihydrochloride (10 or 20 mg/kg/day) experienced adverse reactions. The most commonly reported adverse reactions are “amino acid level decreased” (hypophenylalaninaemia), vomiting and rhinitis.

Tabulated list of adverse reactions

In the pivotal clinical trials and in the post-marketing experience for Kuvan, the following adverse reactions have been identified.

The following definitions apply to the frequency terminology used hereafter:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Frequency not known (cannot be estimated from available data)

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Immune system disorders
Not known: Hypersensitivity reactions (including serious allergic reactions) and rash

Metabolism and nutrition disorders:
Common: Hypophenylalaninaemia

Nervous system disorders:

Very common: Headache

Respiratory, thoracic and mediastinal disorders:
Very common: Rhinorrhoea
Common: Pharyngolaryngeal pain, nasal congestion, cough

Gastrointestinal disorders:
Common: Diarrhoea, vomiting, abdominal pain, dyspepsia, nausea
Unknown: Gastritis

Paediatric population
Frequency, type, and severity of adverse reactions in children were essentially similar to those in adults.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il).

4.9 Overdose

Headache and dizziness have been reported after the administration of sapropterin dihydrochloride 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 in a study with a single supra-therapeutic dose of 100 mg/kg (5 times the maximum recommended dose); this should be taken into consideration in managing patients who have a pre-existing shortened QT interval (e.g. patients with familial short QT syndrome).

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 levels and is usually caused by autosomal recessive mutations in the genes encoding for phenylalanine hydroxylase enzyme (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 cases, phenylalanine cannot be effectively transformed into the amino acid tyrosine, leading to increased phenylalanine levels in the blood.

Sapropterin 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 phenylalanine sufficient to reduce or maintain blood phenylalanine levels, prevent or decrease further phenylalanine accumulation, and increase tolerance to

phenylalanine intake in the diet. The rationale for administration of Kuvan in patients with BH4 Deficiency is to replace the deficient levels of BH4, thereby restoring the activity of phenylalanine hydroxylase.

Clinical efficacy

The Phase III clinical development program for Kuvan included 2, randomised placebo-controlled studies in patients with PKU. The results of these studies demonstrate the efficacy of Kuvan to reduce blood phenylalanine levels and to increase dietary phenylalanine tolerance.

In 88 subjects with poorly controlled PKU who had elevated blood phenylalanine levels at screening, sapropterin dihydrochloride 10 mg/kg/day significantly reduced blood phenylalanine levels as compared to placebo. The baseline blood phenylalanine levels for the Kuvan-treated group and the placebo group were similar, with mean ± SD baseline blood phenylalanine levels of 843 ± 300 µmol/l and 888 ± 323 µmol/l, respectively. The mean ± SD decrease from baseline in blood phenylalanine levels at the end of the 6 week study period was 236 ± 257 µmol/l for the sapropterin treated group (n=41) as compared to an increase of 2.9 ± 240 µmol/l for the placebo group (n=47) ($p<0.001$). For patients with baseline blood phenylalanine levels ≥ 600 µmol/l, 41.9% (13/31) of those treated with sapropterin and 13.2% (5/38) of those treated with placebo had blood phenylalanine levels < 600 µmol/l at the end of the 6-week study period ($p=0.012$).

In a separate 10-week, placebo-controlled study, 45 PKU patients with blood phenylalanine levels controlled on a stable phenylalanine-restricted diet (blood phenylalanine ≤ 480 µmol/l on enrolment) were randomized 3:1 to treatment with sapropterin dihydrochloride 20 mg/kg/day (n=33) or placebo (n=12). After 3 weeks of treatment with sapropterin dihydrochloride 20 mg/kg/day, blood phenylalanine levels were significantly reduced; the mean ± SD decrease from baseline in blood phenylalanine level within this group was 149 ± 134 µmol/l ($p<0.001$). After 3 weeks, subjects in both the sapropterin and placebo treatment groups were continued on their phenylalanine-restricted diets and dietary phenylalanine intake was increased or decreased using standardized phenylalanine supplements with a goal to maintain blood phenylalanine levels at <360 µmol/l. There was a significant difference in dietary phenylalanine tolerance in the sapropterin treatment group as compared to the placebo group. The mean ± SD increase in dietary phenylalanine tolerance was 17.5 ± 13.3 mg/kg/day for the group treated with sapropterin dihydrochloride 20 mg/kg/day, compared to 3.3 ± 5.3 mg/kg/day for the placebo group ($p = 0.006$). For the sapropterin treatment group, the mean ± SD total dietary phenylalanine tolerance was 38.4 ± 21.6 mg/kg/day during treatment with sapropterin dihydrochloride 20 mg/kg/day compared to 15.7 ± 7.2 mg/kg/day before treatment.

Paediatric population

The safety, efficacy and population pharmacokinetics of Kuvan were studied in a multicenter, open-label, randomized, controlled study in children < 4 years old with a confirmed diagnosis of PKU.
56 paediatric PKU patients <4 years of age were randomized 1:1 to receive either 10 mg/kg/day Kuvan 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 Kuvan dose was increased in a single step to 20 mg/kg/day.
The results of this study demonstrated that daily dosing with 10 or 20 mg/kg/day of Kuvan 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 Kuvan 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).

Limited studies have been conducted in patients under 4 years of age with BH4 deficiency using another formulation of the same active substance (sapropterin) or an un-registered preparation of BH4.

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. The absorption of sapropterin is higher after a high-fat, high-calorie meal as compared to fasting, resulting, in average, in 40-85% higher maximum blood concentrations achieved 4 to 5 hours after administration.

Absolute bioavailability or bioavailability for humans after oral administration is not known.

Distribution

In non-clinical studies, sapropterin was primarily distributed to the kidneys, adrenal glands, and liver as assessed by levels of total and reduced biopterin concentrations. In rats, following intravenous radiolabeled sapropterin administration, radioactivity was found to distribute in foetuses. Excretion of total biopterin in milk was demonstrated in rats by intravenous route. No increase in total biopterin concentrations in either foetuses or milk was observed in rats after oral administration of 10mg/kg sapropterin dihydrochloride.

Biotransformation

Sapropterin dihydrochloride is primarily metabolised in the liver to dihydrobiopterin and biopterin. Since sapropterin dihydrochloride is a synthetic version of the naturally occurring 6R-BH4, it can be reasonably anticipated to undergo the same metabolism, including 6R-BH4 regeneration.

Elimination

Following intravenous administration in rats, sapropterin dihydrochloride is mainly excreted in the urine. Following oral administration it is mainly eliminated through 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.

Drug Interactions
Based on an *in vitro* study, there is potential for Kuvan to inhibit p-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) in the gut at the therapeutic doses. The clinical implications of these findings are not known. Co-administration of Kuvan may increase systemic exposure to drugs that are substrates for P-gp or BCRP. *In vitro*, sapropterin did not

inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5, nor induce CYP1A2, 2B6, or 3A4/5.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology (CNS, respiratory, cardiovascular, genitourinary), and toxicity to reproduction.

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.

Sapropterin was found to be weakly mutagenic in bacterial cells and an increase in chromosome aberrations was detected in Chinese hamster lung and ovary cells. However, sapropterin has not been shown to be genotoxic in the *in vitro* test with human lymphocytes as well as in *in vivo* micronucleus mouse tests.

No tumorigenic activity was observed in an oral carcinogenicity study in mice at doses of up to 250 mg/kg/day (12.5 to 50 times the human therapeutic dose range).

Emesis has been observed in both the safety pharmacology and the repeated-dose toxicity studies. Emesis is considered to be related to the pH of the solution containing sapropterin.

No clear evidence of teratogenic activity was found in rats and in rabbits at doses of approximately 3 and 10 times the maximum recommended human dose, based on body surface area.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ascorbic acid
Crospovidone
Dibasic calcium phosphate anhydrous
Mannitol
Riboflavin
Sodium stearyl fumarate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C.
Keep the bottle tightly closed in order to protect from moisture.
Shelf life after first opening –until 2 months

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottle 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 contains 30 or 120 tablets.

1 bottle per carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Disposal

No special requirements.

Handling

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

For instructions for use, see section 4.2: Posology and method of administration.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Manufacturer

BioMarin International Ltd.
Shanbally, Ringaskiddy,
Co. Cork
Ireland

8. MARKETING AUTHORISATION HOLDER

Medison Pharma Ltd.
POB 7090 Petach Tikva
Israel