ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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 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.

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 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.

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 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 should be considered non-responsive, these patients should not be treated with Kuvan and administration of Kuvan should be discontinued.

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 sapropterin 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

The tablets should be administered with a meal as a single daily dose, to increase the absorption, and at the same time each day preferably in the morning.

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) (rounded)
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

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

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

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

<u>After administration:</u> 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

Pregnancy

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.

Disease-associated maternal and/or embryofetal risk available 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 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

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Headache and dizziness have been reported after the administration of sapropterin dihydrochloride above the recommended maximum dose of 20 mg/kg per day. Treatment of overdose should be directed to symptoms.

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 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 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 10 mg/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 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

Mannitol (E421)
Calcium hydrogen phosphate, anhydrous
Crospovidone type A
Ascorbic acid (E300)
Sodium stearyl fumarate
Riboflavin (E101)

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.

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, 120 or 240 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 instrutions 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. MARKETING AUTHORISATION HOLDER

BioMarin International Limited
Shanbally, Ringaskiddy
County Cork
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/481/001
EU/1/08/481/002
EU/1/08/481/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of the first authorisation: 02 December 2008
Date of latest renewal: 02 December 2013

10. DATE OF REVISION OF THE TEXT

Date of revision of the text: MM/YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION OR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

BioMarin International Limited
Shanbally, Ringaskiddy
County Cork
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION OR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

Not aplicable

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON AND BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Kuvan 100 mg soluble tablets
Sapropterin dihydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 soluble tablets
120 soluble tablets
240 soluble tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use, after dissolution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Each bottle of Kuvan contains a small plastic tube of desiccant (silica gel). Do not swallow the tube or the contents.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.
Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioMarin International Limited
Shanbally, Ringaskiddy
County Cork
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/481/001
EU/1/08/481/002
EU/1/08/481/003

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

kuvan

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Kuvan 100 mg soluble tablets
Sapropterin dihydrochloride

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Kuvan is and what it is used for

Kuvan contains the active substance sapropterin which is a synthetic copy of a body's own substance called tetrahydrobiopterin (BH4). BH4 is required by the body to use an amino acid called phenylalanine in order to build another amino acid called tyrosine.

Kuvan is used to treat hyperphenylalaninaemia (HPA) or phenylketonuria (PKU) in adults and children of all ages. HPA and PKU are due to abnormally high levels of phenylalanine in the blood which can be harmful. Kuvan reduces these levels in some patients who respond to BH4 and can help increase the amount of phenylalanine that can be included in the diet.

This medicine is also used to treat an inherited disease called BH4 deficiency in adults and children of all ages, in which the body cannot produce enough BH4. Because of very low BH4 levels phenylalanine is not used properly and its levels rise, resulting in harmful effects. By replacing the BH4 that the body cannot produce, Kuvan reduces the harmful excess of phenylalanine in the blood and increases the dietary tolerance to phenylalanine.

2. What you need to know before you take Kuvan

Do not take Kuvan
If you are allergic to sapropterin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before taking Kuvan, particularly:
- if you are 65 years of age or older
- if you have problems with your kidney or liver
- if you are ill. Consultation with a physician is recommended during illness as blood phenylalanine levels may increase
- if you have predisposition to convulsions

When you are treated with Kuvan, your doctor will test your blood to verify how much phenylalanine and

tyrosine it contains and may decide to adjust the dose of Kuvan or your diet if needed.
You must continue your diet treatment as recommended by your doctor. Do not change your diet without contacting your doctor. Even if you take Kuvan, if your phenylalanine blood levels are not well controlled, you can develop severe neurologic problems. Your doctor should continue to monitor your blood phenylalanine levels often during your treatment with Kuvan, **to make sure that your blood phenylalanine levels are not too high or too low.**

Other medicines and Kuvan
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. In particular you should tell your doctor if you are using:
- levodopa (used to treat Parkinson's disease)
- medicines for treatment of cancer (e.g.methotrexate)
- medicines for treatment of bacterial infections (e.g. trimethoprim)
- medicines that cause dilation of blood vessels, (such as glyceryl trinitrate (GTN), isosorbide dinitrate (ISDN), sodium nitroprusside (SNP),molsidomin, minoxidil).

Pregnancy and breast feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

If you are pregnant your doctor will tell you how to control phenylalanine levels adequately. If these are not strictly controlled before or when you become pregnant, this could be harmful to you and to your baby. Your doctor will monitor the restriction of dietary phenylalanine intake prior and during pregnancy.

If the strict diet does not adequately reduce phenylalanine amount in your blood your doctor will consider whether you must take this medicine.

You should not take this medicine if you are breast-feeding.

Driving and using machines
Kuvan is not expected to affect the ability to drive and use machines.

Important information about some of the ingredients of Kuvan
This medicine contains less than 1 mmol (23 mg) sodium per tablet, i.e. essentially "sodium-free".

3. How to take Kuvan

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

PKU
The recommended starting dose of Kuvan in adults and children with PKU is 10 mg for each kg of body weight. Take the soluble tablets as a single daily dose with a meal to increase the absorption, and at the same time each day, preferably in the morning. Your doctor may adjust your dose, usually between 5 and 20 mg for each kg of body weight per day, depending on your condition.

BH4 deficiency
The recommended starting dose of Kuvan in adults and children with BH4 deficiency is 2 to 5 mg for each kg of body weight. Take the soluble tablets as a single daily dose, with a meal to increase the absorption, and at the same time each day, preferably in the morning. Your doctor may adjust your dose up to 20 mg for each kg of body weight per day, depending on your condition. It may be necessary to divide the total daily dose into 2 or 3 doses, distributed over the day, to achieve the best therapeutic effect.

The table below is an example of how an appropriate dose is calculated

Body weight (kg)	Number of tablets (Kuvan dose 10 mg/kg)	Number of tablets (Kuvan dose 20 mg/kg)
10	1	2
20	2	4
30	3	6
40	4	8
50	5	10

Method of administration

Use in all patients
Place the prescribed number of tablets in a glass or cup of water as accurately described below and stir until dissolved.

It may take a few minutes for the tablets to dissolve. To make the tablets dissolve faster you can crush them. Small particles may be visible in the solution, but they will not affect the effectiveness of the medicine. Drink the dissolved preparation of Kuvan with a meal, at the same time each day, preferably in the morning within 15 to 20 minutes of its preparation.

Do not swallow the desiccant capsule contained in the bottle.

Use in adults
Place the tablets in a glass or cup (120 to 240 ml) of water and stir until dissolved.

Use in children above 20 kg body weight
Place the prescribed number of tablets in a glass or cup (up to 120 ml) of water and stir until dissolved.

Use in children up to 20 kg body weight
The dose of Kuvan is based on body weight. This will change as your child grows. Your doctor will tell you:
- the number of Kuvan tablets needed for one dose
- the amount of water needed to mix one dose of Kuvan
- the amount of solution you will need to give your child for their prescribed dose

Your child should drink the dissolved preparation of Kuvan with a meal, at the same time each day, preferably in the morning. Give your child the prescribed amount of solution within 15 to 20 minutes after dissolving. If you are not able to give your child's dose within 15 to 20 minutes after dissolving the tablets, pour the unused medicine into the trash. You will need to prepare a new solution as the unused solution should not be used beyond 20 minutes.

Supplies needed to prepare and give your child's dose of Kuvan
- The number of Kuvan tablets needed for one dose
- A medicine cup with graduation markings at 20, 40, 60 and 80 ml
- A glass or cup
- Small spoon or clean utensil for stirring
- Oral dosing syringe (graduated in 1 ml divisions) (10 ml syringe for administration of volumes of ≤10 ml or 20 ml syringe for administration of volumes of >10 ml)

Ask your doctor for the medicine cup for dissolving the tablets and the 10 ml or 20 ml oral dosing syringe if you do not have these supplies.

Place the prescribed number of tablets in the medicine cup. Pour the amount of water into the medicine cup, as instructed by your doctor (e.g. your doctor told you to use 20 ml for dissolving one Kuvan tablet). Check to make sure that the amount of liquid lines up with the amount that your doctor tells you. Stir with the small spoon or clean utensil until the tablets dissolve.

If your doctor told you to administer only a portion of the solution, point the tip of the oral dosing syringe into the medicine cup. Slowly pull back the plunger to withdraw the amount as instructed by your doctor. Transfer the solution by pushing on the plunger slowly until all of the solution in the oral dosing syringe is transferred to a glass or cup for administration (e.g. if your doctor told you to dissolve two Kuvan tablets in 40 ml water and administer 30 ml to your child, you would have to use the 20 ml oral dosing syringe two times to draw up 30 ml (e.g. 20 ml + 10 ml) Kuvan solution and transfer it to a glass or cup for administration). Use a 10 ml oral dosing syringe for administration of volumes ≤10 ml or a 20 ml oral dosing syringe for administration of volumes >10 ml.

If your baby is too small to drink from a glass or a cup you may administer the dissolved preparation of Kuvan via the oral dosing syringe. Draw up the prescribed volume from the solution prepared in the medicine cup and place the tip of the oral dosing syringe into your baby's mouth. Point the tip of the oral dosing syringe towards either cheek. Push on the plunger slowly, a small amount at a time, until all of the solution in the oral dosing syringe is given.

Throw away any remaining solution. 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.

If you take more Kuvan than you should
If you take more Kuvan than prescribed, you may experience side effects that could include headache and dizziness. Immediately contact your doctor or pharmacist if you take more Kuvan than prescribed.

If you forget to take Kuvan
Do not take a double dose to make up for a forgotten dose. Take the next dose at the usual time.

If you stop taking Kuvan
Do not stop taking Kuvan without prior discussion with your doctor, as phenylalanine levels in your blood may increase.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Few cases of allergic reactions (such as skin rash and serious reactions) have been reported. Their frequency is not known (frequency cannot be estimated from the available data).
If you have red, itchy, raised areas (hives), runny nose, fast or uneven pulse, swelling of your tongue and throat, sneezing, wheezing, serious difficulty in breathing or dizziness, you may be having a serious allergic reaction to the medicine. If you notice these signs, contact your doctor immediately.

Very common side effects (may affect more than 1 in 10 people)
Headache and runny nose.

Common side effects (may affect up to 1 in 10 people)
Sore throat, nasal congestion or stuffy nose, cough, diarrhoea, vomiting, stomach ache and too low levels of phenylalanine in blood tests (see section 2: Warnings and precautions).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Kuvan

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle and the carton after “EXP”. The expiry date refers to the last day of that month.

Store below 25°C.
Keep the bottle tightly closed in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Kuvan contains
- The active substance is sapropterin dihydrochloride. Each tablet contains 100 mg of sapropterin dihydrochloride (equivalent to 77 mg of sapropterin).
- The other ingredients are mannitol (E421), calcium hydrogen phosphate anhydrous, crospovidone type A, ascorbic acid (E300), sodium stearyl fumarate, and riboflavin (E101).

What Kuvan looks like and contents of the pack
Kuvan 100 mg soluble tablets are off-white to light yellow with “177” imprinted on one face.

It is available in bottles with child-resistant closure of 30, 120 or 240 soluble tablets. Each bottle contains a small plastic tube of desiccant (silica gel).

Not all pack sizes may be marketed.

Marketing Authorisation Holder
BioMarin International Limited
Shanbally, Ringaskiddy
County Cork
Ireland

Manufacturer
BioMarin International Limited
Shanbally, Ringaskiddy
County Cork
Ireland

This leaflet was last revised in month/YYYY

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.