SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sapropterin Dihydrochloride 100 mg powder for oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Sapropterin Dihydrochloride 100 mg powder for oral solution

Each sachet contains 100 mg of sapropterin dihydrochloride equivalent to 77 mg of sapropterin.

Excipient(s) with known effect
Each sachet contains 0.3 mmol (11.7 mg) potassium.

Excipient(s) with known effect
Each sachet contains 1.6 mmol (62.6 mg) potassium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for oral solution.

White to yellowish powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Sapropterin Dihydrochloride 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).

Sapropterin Dihydrochloride 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 sapropterin dihydrochloride 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 this medicinal product 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, Sapropterin Dihydrochloride is intended for long-term use (see section 5.1).

Posology

PKU
The starting dose of sapropterin dihydrochloride 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 sapropterin dihydrochloride 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 a total of 20 mg/kg per day.

For patients above 20 kg body weight, the calculated daily dose based on body weight should be rounded to the nearest multiple of 100 mg.

Dose adjustment
Treatment with sapropterin may decrease blood phenylalanine levels below the desired therapeutic level. Adjustment of the sapropterin dihydrochloride 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 the paediatric population, one to two weeks after each dose adjustment and monitored frequently thereafter, under the direction of the treating physician.

If inadequate control of blood phenylalanine levels is observed during treatment with sapropterin dihydrochloride, the patient’s adherence to the prescribed treatment, and diet, should be reviewed before considering an adjustment of the dose of sapropterin.

Discontinuation of 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.

Determination of response
It is of primary importance to initiate 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 this medicinal product is determined by a decrease in blood phenylalanine.Blood phenylalanine levels should be checked before administering sapropterin dihydrochloride and after 1 week of use at the recommended starting dose. If an unsatisfactory reduction in blood phenylalanine levels is observed, then the dose 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 $\geq$ 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 sapropterin dihydrochloride and administration of sapropterin dihydrochloride should be discontinued.

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

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 sapropterin dihydrochloride 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).

Special populations

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

Renal or hepatic impairment
Safety and efficacy of sapropterin dihydrochloride in patients with renal or hepatic insufficiency have not been established. Caution must be exercised when prescribing to such patients.

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

Method of administration

Oral use.

Sapropterin Dihydrochloride should be administered with a meal, to increase the absorption.

For patients with PKU, Sapropterin Dihydrochloride 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.

The solution should be consumed within 30 minutes of initial dissolution. Unused solution should be discarded after administration.

The prescribed dose of Sapropterin Dihydrochloride powder for oral solution dissolved in water, may be administered via an enteral feeding tube ≥4 Fr (French catheter scale). Follow the manufacturer's instructions for the feeding tube to administer the medicinal product. To ensure adequate dosing, after administration of the oral solution, the enteral feeding tube must be flushed with water. See section 6.6 for further details.

Patients above 20 kg body weight
The contents of the sachet(s) should be placed in 60 to 240 ml of water or apple juice and stirred until dissolved. The powder for oral solution may also be mixed in a small amount of soft foods, such as apple sauce or pudding.

Children up to 20 kg body weight (use only 100 mg powder sachets)
The measuring devices required for dosing in children up to 20 kg body weight (i.e. cup with graduations at 20, 40, 60, 80 ml; 10 ml and 20 ml oral syringes with graduation at 1 ml divisions) are not included in the Sapropterin Dihydrochloride pack. These devices are supplied to the specialised paediatric centres for inborn errors of metabolism to be provided to the caregivers of the patients.

The appropriate number of 100 mg sachet(s) should be dissolved in a volume of water or apple juice depicted in Tables 1-4 based on the prescribed total daily dose. For dosage equal to 100 mg and multiples of 100 mg, the powder for oral solution may also be mixed in a small amount of soft foods, such as apple sauce or pudding.

If only a portion of this solution needs to be administered, an oral syringe should be used to withdraw the volume of solution to be administered. The solution may then be transferred to another cup for administration of the medicinal product. For small infants, an oral syringe can be used. A 10 ml oral syringe should be used for administration of volumes of ≤ 10 ml and a 20 ml oral syringe for administration of volumes of > 10 ml.

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

Weight (kg)	Total dose (mg/day)	Number of sachets to be dissolved (100 mg strength only)	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 30 minutes for powder 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 sachets to be dissolved (100 mg strength only)	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 30 minutes for powder 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 sachets to be dissolved (100 mg strength only)	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 30 minutes for powder 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 sachets to be dissolved (100 mg strength only)	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 30 minutes for powder solution.

For cleaning, the plunger should be removed from the barrel of the oral syringe. Both parts of the oral syringe and the cup should be washed with warm water and air dry. When the oral syringe is dry, the plunger should be put back into the barrel. The oral syringe and the cup should be stored 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 sapropterin dihydrochloride 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 sapropterin dihydrochloride 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 sapropterin dihydrochloride 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.

Potassium content

Sapropterin Dihydrochloride 100 mg powder for oral solution
This medicinal product contains 0.3 mmol (11.7 mg) potassium per sachet. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

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 sapropterin dihydrochloride.

BH4 is a cofactor for nitric oxide synthetase. Caution is recommended during concomitant use of sapropterin dihydrochloride 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 sapropterin dihydrochloride 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 sapropterin dihydrochloride 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 sapropterin dihydrochloride 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. sapropterin dihydrochloride 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

Sapropterin Dihydrochloride 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 sapropterin 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 sapropterin, 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), 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
Not known: Gastritis, oesophagitis

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 Yellow Card Scheme.
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 sapropterin dihydrochloride 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 sapropterin dihydrochloride 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 sapropterin included 2, randomised placebo-controlled studies in patients with PKU. The results of

these studies demonstrate the efficacy of sapropterin 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 sapropterin-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 randomised 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 standardised 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 sapropterin in paediatric patients aged < 7 years were studied in two open-label studies.

The first study 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 in conjunction with 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 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 sapropterin in conjunction with a 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 in conjunction with a phenylalanine-restricted diet 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 sapropterin treatment in conjunction with a phenylalanine-restricted diet, demonstrating sustained benefit over 3.5 years.

The second study was a multicenter, uncontrolled, open-label study designed to evaluate the safety and effect on preservation of neurocognitive function of sapropterin 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 sapropterin; 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 sapropterin. Patients with pre-existing neurocognitive damage (IQ < 80) were excluded from the study. Ninety-three 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= 27), WPPSI-III score (101, SD= 11, n= 34) 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 sapropterin in children less than 7 years of age.

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 (Cmax) 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

In vitro studies

In vitro, sapropterin did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5, nor induce CYP1A2, 2B6, or 3A4/5.

Based on an *in vitro* study, there is potential for sapropterin dihydrochloride to inhibit p-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) in the gut at the therapeutic doses. A higher intestinal concentration of sapropterin is needed to inhibit BCRP than P-gp, as inhibitory potency in intestine for BCRP (IC50= 267 µM) is lower than P-gp (IC50= 158 µM).

In vivo studies

In healthy subjects, administration of a single dose of sapropterin 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. Based on the in vitro and in vivo results, co-administration of sapropterin is unlikely to increase systemic exposure to drugs that are substrates for BCRP.

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)
Potassium citrate (E332)
Sucralose (E955)
Ascorbic acid (E300)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polyethylene terephthalate, aluminium, polyethylene laminate sachet, heat sealed on four sides. An internal tear notch is located in the corner of the sachet to facilitate opening of the sachet.

Each carton contains 30 sachets.

6.6 Special precautions for disposal

Disposal

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

Preparation and handling

Sapropterin Dihydrochloride powder for oral solution should be placed in water or apple juice and stirred until dissolved. The powder for oral solution may also be mixed in a small amount of soft foods (such as apple sauce or pudding). Upon dissolving Sapropterin Dihydrochloride powder for oral solution in water, the solution has a clear, colourless to yellow appearance. The preparation should be administered within 30 minutes. For instructions for use, see section 4.2.

Administration via an enteral feeding tube

The prescribed dose of Sapropterin Dihydrochloride powder for oral solution, dissolved in water, may be administered via an enteral feeding tube ≥4 Fr (French catheter scale). In case of administration using an enteral feeding tube, an appropriate commercially available tube should be selected by the healthcare professional. Nasogastric feeding tube tubes made of polyvinylchloride (PVC) and polyurethane (PUR), and PEG feeding tube made of silicone have been shown compatible with the oral solution. The tube size considered as appropriate for the intended use and age group, is 4 to 18 Fr, i.e. small to medium tubes for the feeding of paediatric patients and adults. Follow the manufacturer's instructions for the feeding tube to administer the medicinal product. To ensure adequate dosing, after administration of the oral solution, the enteral feeding tube must be flushed with water. The recommended enteral feeding tube size and flush volumes to achieve a full dose are provided in the table below.

Table 5: Recommended enteral feeding tube size and flush volume

Recommended tube size (diameter)	Recommended flush volume (based on the tube with a length of)
4 Fr	1 ml (50 cm)
8 Fr	10 ml (125 cm)
10 Fr	15 ml (100 cm)
18 Fr	40 ml (125 cm)

7 MARKETING AUTHORISATION HOLDER

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