

New Zealand Data Sheet

Sapropterin Dipharma

Sapropterin dihydrochloride

1. PRODUCT NAME

Sapropterin Dipharma 100 mg soluble tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soluble tablet contains 100 mg of sapropterin dihydrochloride (equivalent to 76.8 mg of sapropterin).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soluble tablet

White to off-white colored circular tablet with "11" imprinted on one face and breakline on the other side.

The score line is not intended for breaking the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sapropterin Dipharma is indicated for the treatment of hyperphenylalaninemia (HPA) in sapropterin-responsive adult and paediatric patients with phenylketonuria (PKU) or tetrahydrobiopterin (BH4) deficiency (see 4.2 DOSE AND METHOD OF ADMINISTRATION) for definition of sapropterin responsiveness).

4.2 Dose and method of administration

Treatment with Sapropterin Dipharma must be initiated and supervised by a physician experienced in the treatment of PKU and BH4 deficiency. Sapropterin Dipharma should be administered with a meal as a single daily dose, at the same time each day, preferably in the morning.

Active management of dietary phenylalanine and overall protein intake while taking Sapropterin Dipharma 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 Dipharma is intended for long-term use. However, there are limited data regarding the long-term use of Sapropterin Dipharma.

Cessation of treatment must be conducted with close physician observation and monitoring due to the possibility of rebound in blood phenylalanine levels above pre-treatment levels (see 4.8 UNDESIRABLE EFFECTS).

Dosage

Sapropterin Dipharma is provided as 100 mg tablets. For doses above 100 mg, 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.

For doses below 100 mg, one tablet should be dissolved in 100 mL of water and the volume of solution corresponding to the prescribed dose administered. An accurate measuring device with suitable graduations should be used to ensure administration of the appropriate volume of solution. Any unused portion should be discarded.

PKU

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

BH4 deficiency

The starting dose of Sapropterin Dipharma in adult and paediatric patients with BH4 deficiency is 2 to 5 mg/kg body weight once daily. The dose is adjusted to achieve and maintain

adequate blood phenylalanine levels as defined by the physician. The recommended daily dose is between 2 and 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.

Determination of Response

Response to treatment is determined by a decrease in blood phenylalanine following treatment with Sapropterin Dipharma. Blood phenylalanine levels should be checked before initiating treatment and after 1 week of treatment with Sapropterin Dipharma at the recommended starting dose. If an unsatisfactory reduction in blood phenylalanine levels is observed, then the dose of Sapropterin Dipharma 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 and should not receive further treatment with Sapropterin Dipharma.

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

Method of administration

Compared to fasting, absorption of sapropterin is higher after a high-fat, high-calorie meal, resulting, on average, in 40-85% higher maximum blood concentrations achieved 4 to 5 hours after administration. To increase absorption, tablets should be administered as a single daily dose with a meal, at the same time each day preferably in the morning.

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 drunk within 15 to 20 minutes.

Limited information is available on administering sapropterin dihydrochloride in solutions other than water and no information is available on administering it in formula or milk. Because of the possibility that absorption may be affected, only water should be used to prepare and administer Sapropterin Dipharma.

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 Patients

For doses above 100 mg, the prescribed number of tablets should be placed in a glass or cup with up to 120 mL of water and stirred until dissolved.

For doses below 100 mg, one tablet should be dissolved in 100 mL of water and the volume of solution corresponding to the prescribed dose administered. An accurate measuring device with suitable graduations should be used to ensure administration of the appropriate volume of solution. Any unused portion should be discarded.

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

Sapropterin Dipharma tablets can be dissolved in smaller volumes should this be required for particular patients, e.g. young children. The minimum volume of solution required to dissolve each tablet is 20 mL, i.e. 1 tablet in 20 mL, 2 tablets in 40 mL, and so on.

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

Monitoring

Treatment with Sapropterin Dipharma may decrease blood phenylalanine levels below the desired therapeutic level. Adjustment of the Sapropterin Dipharma 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 Sapropterin Dipharma, the patient's adherence to the prescribed treatment, and diet, should be reviewed before considering an adjustment of the dose of Sapropterin Dipharma.

Discontinuation of Sapropterin Dipharma 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.

4.3 Contraindications

Sapropterin Dipharma is contraindicated in patients with hypersensitivity to sapropterin or to any of the excipients (See 6.1 LIST OF EXCIPIENTS).

4.4 Special warnings and precautions for use

PRECAUTIONS

The safety and efficacy of sapropterin dihydrochloride in paediatric patients less than 4 years of age have not been established in controlled clinical trials.

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

Sapropterin Dipharma does not work in all patients with PKU or BH4 deficiency but only in those who have shown a definite response. Response to treatment cannot be predetermined by laboratory testing (e.g. genetic testing) but can only be determined by a therapeutic trial of Sapropterin Dipharma (see 4.2 DOSE AND METHOD OF ADMINISTRATION).

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

Sustained or recurrent dysfunction in the phenylalanine-tyrosine-dihydroxy-L-phenylalanine (DOPA) metabolic pathway can result in deficient body protein and neurotransmitter synthesis. Prolonged elevations in blood phenylalanine levels in patients with PKU and BH4 deficiency can result in severe neurologic damage, including severe mental retardation, microcephaly, delayed speech, seizures, and behavioural abnormalities. This may occur even if patients are taking Sapropterin Dipharma but not adequately controlling their blood phenylalanine levels within the recommended target range. Conversely, prolonged exposure to low blood phenylalanine and tyrosine levels during infancy has been associated with impaired neurodevelopmental outcome. Active management of dietary phenylalanine and overall protein intake while taking Sapropterin Dipharma is required to ensure adequate control of blood phenylalanine and tyrosine levels and nutritional balance.

It is of primary importance to initiate Sapropterin Dipharma 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.

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

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

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

There are limited data regarding the long-term use of sapropterin dihydrochloride

Renal and 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 patients with renal or hepatic insufficiency.

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

Paediatric Use

Paediatric patients, 4 years of age and older, with HPA due to PKU and BH4 deficiency have been treated with Sapropterin dihydrochloride in clinical studies.

Sapropterin dihydrochloride has not been specifically studied in PKU children under 4 years of age. Published literature indicates that more than 2,700 children with PKU aged newborn to 4 years have been administered BH4, including at least 43 who received therapy for 2 months or longer. BH4 deficiency is an extremely rare condition but reports of published studies include at least 120 patients starting treatment when less than 4 years of age.

Data from toxicity studies in juvenile and adult rats are suggestive of an inverse relationship between age and the oral absorption rate of sapropterin dihydrochloride. Microscopic changes occurred in kidneys in the early postnatal period at lower sapropterin doses than the ones causing similar effects in adult rats, most likely related to this absorption rate effect. In addition, sapropterin and/or its metabolites were distributed to the brain to a much greater extent in young rats compared to adult rats.

Pharmacokinetic studies of sapropterin dihydrochloride in children less than 4 years of age are not available. Prescribers should use caution when dosing children, particularly infants, as the absorption rate may be higher in this population. Frequent blood monitoring is recommended to maintain adequate blood phenylalanine levels as defined by the physician.

Use in the Elderly

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

Carcinogenicity

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

Genotoxicity

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

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

4.5 Interaction with other medicines and other forms of interaction

No specific drug-drug interaction studies have been performed.

Although concomitant administration of inhibitors of dihydrofolate reductase (e.g. methotrexate, trimethoprim) has not been studied, such medicinal products may interfere with BH4 metabolism. Caution is recommended when using such agents during treatment with Sapropterin Dipharma.

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

Caution should be exercised when prescribing Sapropterin Dipharma to patients receiving treatment with levodopa, as increased excitability and irritability has been reported during concomitant use.

Events of convulsion and exacerbation of convulsion have been observed during co-administration of levodopa and sapropterin dihydrochloride in BH4-deficient patients.

4.6 Fertility, pregnancy and lactation

Effects on Fertility

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

Use in Pregnancy (Pregnancy Category B1)

For sapropterin dihydrochloride, no clinical data on exposed pregnancies are available.

Maternal blood phenylalanine levels must be strictly controlled before and during pregnancy. If maternal phenylalanine levels are not strictly controlled before and during pregnancy, this could be harmful to the mother and the fetus. Uncontrolled levels of phenylalanine, above 600 μ mol/L in pregnant women, have been associated with a very high incidence of neurological, cardiac, facial dysmorphism and growth anomalies in their infants. Physician-supervised restriction of dietary phenylalanine intake prior to and throughout pregnancy is the first choice of treatment in this patient group.

In rats, following intravenous administration of radiolabelled sapropterin, radioactivity was found to be distributed in fetuses. No increase in total biopterin concentrations in fetuses was observed in rats after oral administration of 10 mg/kg sapropterin dihydrochloride. However, in pregnant guinea pigs there was a marked increase in sapropterin and/or its metabolites in the fetus after oral administration of 20 mg/kg sapropterin dihydrochloride.

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

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

Use in Lactation

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

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

Table 1 shows by preferred term the number and percentage of 74 patients with PKU who had treatment-emergent adverse events (regardless of relationship) that occurred in at least 4% of patients following exposure to sapropterin dihydrochloride at doses of 10 to 20 mg/kg/day for 6 to 10 weeks in 2 double-blind, placebo-controlled clinical trials.

Table 1: Treatment-emergent adverse events with an incidence \geq 4% in patients following exposure to sapropterin dihydrochloride in controlled clinical studies

System Organ Class	Preferred Term	sapropterin dihydrochloride n=74 n (%)	Placebo n=59 n (%)
Any adverse event		47 (64)	42 (71)
Nervous system disorders	Headache	11 (15)	8 (14)
Infections and infestations	Upper respiratory tract infection ¹	9 (12)	14 (24)

Respiratory disorders	Rhinorrhoea	8 (11)	0
	Pharyngolaryngeal pain	7 (10)	1 (2)
	Cough	5 (7)	3 (5)
	Nasal congestion	3 (4)	0
Gastrointestinal disorders	Diarrhoea	6 (8)	3 (5)
	Vomiting	6 (8)	4 (7)
	Abdominal pain	4 (5)	5 (8)
General disorders and administration site conditions	Pyrexia ¹	5 (7)	4 (7)
Injury, poisoning and procedural complications	Contusion ¹	4 (5)	1 (2)
Skin and subcutaneous tissue disorders	Rash ¹	4 (5)	4 (7)

¹ Causal association with sapropterin dihydrochloride is considered unlikely

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

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

Post-marketing Experience

Few cases of hypersensitivity reactions (including rash) have been observed in the post marketing setting.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

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.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Hyperphenylalaninaemia (HPA) is diagnosed as an abnormal elevation in blood phenylalanine (Phe) levels and is usually caused by autosomal recessive mutations in the genes encoding for the liver

enzyme phenylalanine hydroxylase (in the case of phenylketonuria, PKU) or for the enzymes involved in 6R-tetrahydrobiopterin (6R-BH4) biosynthesis or regeneration (in the case of BH4 deficiency). BH4 deficiency is a group of disorders arising from mutations or deletions in the genes encoding for one of the five enzymes involved in the biosynthesis or recycling of BH4.

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

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

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

In PKU patients who are responsive to BH4 treatment, blood Phe levels decrease within 24 hours after a single administration of Sapropterin Dipharma, although maximal effect on Phe level may take up to a month, depending on the patient.

A single daily dose of Sapropterin Dipharma is adequate to maintain stable blood Phe levels over a 24-hour period. In a sub-study of the clinical trial described as 'Study 3' under CLINICAL TRIALS, blood Phe levels were measured multiple times over a 24-hour period in 12 patients taking 10 mg/kg/day. The blood Phe levels remained stable during the 24-hour observation period: mean (\pm Standard Deviation) was 661 (\pm 433) μ mol/L at pre-dose and 631 (\pm 454) μ mol/L at 24 hours post-dose; the lowest mean value during the 24-hour period was 477 (\pm 241) μ mol/L at 16 hours post-dose. No consistent relationship between meals and blood Phe levels was observed during the 24-hour period.

5.2 Pharmacokinetic properties

Absorption

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

Distribution

In non-clinical studies, sapropterin was primarily distributed to the kidneys, liver, adrenal glands and spleen as assessed by levels of total and reduced biopterin concentrations (see also 4.4 Special warnings and precautions for use, 4.6 Fertility, pregnancy and lactation). Very small amounts of sapropterin were distributed to the brain in adult rats but in juvenile rats total brain biopterin levels were significantly increased following sapropterin administration.

Metabolism

6R-BH4 is primarily metabolised in the liver with dihydrobiopterin and dihydroxanthopterin as the main human metabolites. Since sapropterin is a synthetic version of the naturally occurring 6R-BH4, it can be reasonably anticipated to undergo the same metabolism, including 6R-BH4 regeneration. Folic acid and vitamin B12 may increase BH4 levels.

Excretion

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

5.3 Clinical Trials

Phenylketonuria (PKU)

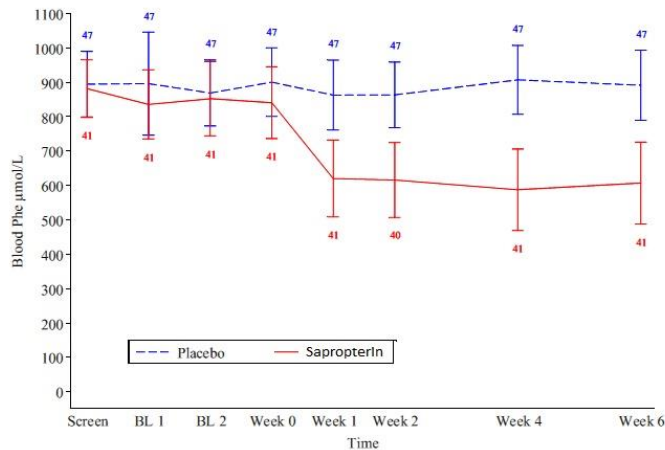
The efficacy and safety of sapropterin dihydrochloride were evaluated in 4 clinical trials in patients with PKU ranging in age from 4 to 48 years old. Patients with significant concurrent diseases with potential to interfere with efficacy and safety analyses were excluded from the trials. The results of these studies demonstrate the efficacy of sapropterin dihydrochloride to reduce blood Phe levels and to increase dietary Phe tolerance.

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

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

The results showed that sapropterin dihydrochloride 10 mg/kg/day significantly reduced blood Phe levels as compared to placebo (See Figure 1). The baseline blood Phe levels for the sapropterin dihydrochloride -treated group and the placebo group were similar, with mean (\pm SD) baseline blood Phe levels of 843 (\pm 300) $\mu\text{mol/L}$ and 888 (\pm 323) $\mu\text{mol/L}$, respectively. The mean (\pm SD) decrease from baseline in blood Phe levels at the end of the 6-week study period was 236 (\pm 257) $\mu\text{mol/L}$ for the sapropterin dihydrochloride treated group as compared to an increase of 3 (\pm 240) $\mu\text{mol/L}$ for the placebo group ($p < 600 \mu\text{mol/L}$ at the end of the 6-week study period ($p=0.012$)).

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



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

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

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

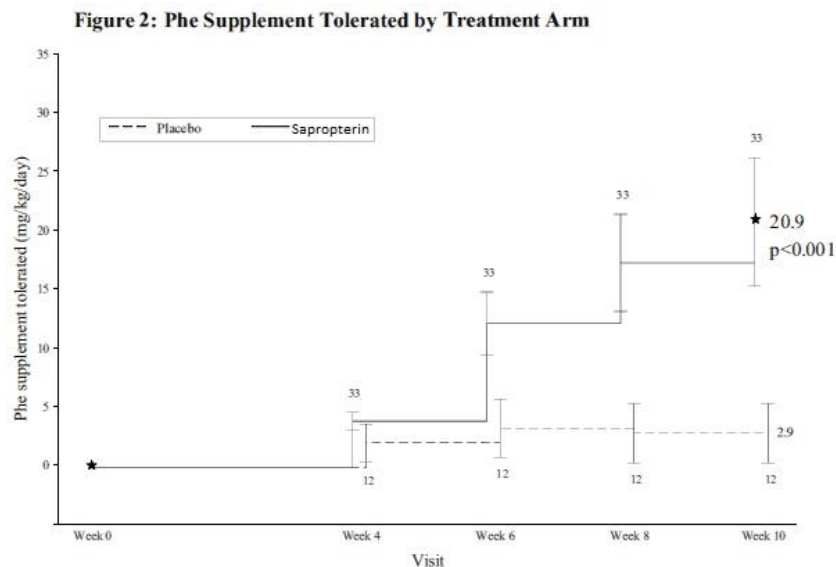
The mean (\pm SD) blood Phe levels at the Weeks 12-22 visits ranged between 620 (\pm 371) and 652 (\pm 383) μ mol/L. On average, patients maintained a stable reduction in Phe levels. The 95% confidence interval for the mean change from baseline blood Phe level at the first visit after subjects started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

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

sapropterin dihydrochloride was defined as a $\geq 30\%$ decrease in blood Phe from baseline and blood Phe $\leq 300 \mu\text{mol/L}$ at Day 8. At Day 8, 50 patients (56%) had a $\geq 30\%$ decrease in blood Phe and blood Phe level $\leq 300 \mu\text{mol/L}$ on Day 8 and were therefore eligible to enrol in the second part of the study.

The second part of Study 4 was a randomised, double-blind, placebo-controlled trial in which subjects were randomised 3:1 to treatment with sapropterin dihydrochloride 20 mg/kg/day (n=34) or placebo (n=12) for 10 weeks. Of the 33 patients who received at least one dose of sapropterin dihydrochloride, 16 (48.5%) were 4-7 years old, 15 (45.5%) were 8-11 years old and the remaining 2 (6.0%) were 12 years old. After 3 weeks of treatment with sapropterin dihydrochloride 20 mg/kg/day, blood Phe levels were significantly reduced; the mean (\pm SD) decrease from baseline in blood Phe level within this group was 149 (\pm 134) $\mu\text{mol/L}$ ($p < 360 \mu\text{mol/L}$). The mean (\pm SD) increase in dietary Phe tolerance was 17.5 (\pm 13.3) mg/kg/day for the sapropterin dihydrochloride group compared to 3.3 (\pm 5.3) mg/kg/day for the placebo group ($p=0.006$). For the sapropterin dihydrochloride treatment group, the mean (\pm SD) total dietary Phe tolerance was 38.4 (\pm 21.6) mg/kg/day during treatment with sapropterin dihydrochloride compared to 15.7 (\pm 7.2) mg/kg/day before treatment.

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



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

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

Patients less than 4 years of age were not included in the sapropterin dihydrochloride clinical trials described above. However, reports in published literature indicate that more than 2,700 children with PKU aged newborn to 4 years of age have been administered BH4, including at least 43 who

received therapy for 2 months or longer. The maximum daily dose reported was 20 mg/kg body weight.

BH4 Deficiency

Evidence of the safety and effectiveness of sapropterin dihydrochloride for the treatment of HPA due to BH4 deficiency is provided by the results of analysis of data from a study conducted with sapropterin dihydrochloride, results from studies conducted with sapropterin dihydrochloride granules registered in Japan for this indication, and published studies of clinical experience with BH4 identified via a systematic literature review. Clinical experience reported in published literature includes prospective and retrospective open-label studies, using both Phe blood levels and clinical outcomes (e.g. IQ and development measures), to determine efficacy. Approximately 120 patients were less than 4 years old at start of treatment, including 104 who started treatment when less than 1 year old. An open-label, multicentre clinical trial evaluating the efficacy and safety of sapropterin dihydrochloride for the treatment of HPA due to BH4 deficiency enrolled 12 patients, 9 with defects in enzymes of BH4 biosynthesis and 3 with defects in enzymes involved in BH4 recycling. Patients ranged in age from 3 to 35 years, 1 (8%) less than 4 years, 3 (25%) between 4-7 years, 2 (17%) between 8-11 years, and the remaining 6 patients (50%) were 12 years of age or older.

Patients receiving an unregistered formulation of BH4 prior to study entry started treatment with sapropterin dihydrochloride at approximately the same daily dose as the prior BH4 dose; other patients commenced treatment at 5 mg/kg/day. Dose adjustment up or down to a maximum of 20 mg/kg/day was permitted at study Week 6. Mean (\pm SD) blood Phe remained at levels similar to baseline ($133 \pm 135 \mu\text{mol/L}$) at all study visits during treatment with sapropterin dihydrochloride. Most subjects remained below the blood Phe target of $< 360 \mu\text{mol/L}$ at all study visits, including all patients with defects in enzymes of BH4 biosynthesis.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ascorbic acid

Sodium stearyl fumarate

Copovidone

Mannitol (E421)

Crospovidone

Riboflavin (E101)

Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf-life from date of manufacture: 3 years

6.4 Special precautions for storage

Store below 25°C.

Keep the bottle tightly closed in order to protect from moisture and light.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottle with polypropylene child-resistant closure. Each bottle contains a canister as desiccant (silica gel)

Each bottle contains 30, 60 or 120 tablets.

1 bottle per carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Supplied in New Zealand under license of Dipharma SA by:

Te Arai BioFarma Ltd

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Wellsford, 0975

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9. DATE OF FIRST APPROVAL

31/5/2018

10. DATE OF REVISION OF THE TEXT

To be completed