Inpheno Tablets 100 mg

1. NAME OF MEDICINAL PRODUCT

Inpheno Tablets 100 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 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.
Light yellow, round, flat-faced tablets, scored on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin deficiency.
Tetrahydrobiopterin-responsive phenylketonuria (PKU).

4.2 Posology and method of administration

Therapy should be directed by physicians who are knowledgeable in the management of hyperphenylalaninemia caused by tetrahydrobiopterin deficiency and tetrahydrobiopterin responsive PKU.
The appropriate dose must be found using dose titration following a phenylalanine load. The dose given depends on the type and degree of hyperphenylalaninemia. The normal dose range is 1-20 mg/kg/d *(Blau & Burgard 2005)*. Phenylalanine levels should be decreased to an acceptable level following oral administration of sapropterin dihydrochloride.
The criteria for dosage are:
Serum phenylalanine within acceptable range (<300 µmol/l (5 mg/dl))
Urine neopterin nearly normal (<5 mmol/mol creati-nine)
Disappearance of reversible neurological symptoms
Urine serotonin normal (>70 µmol/mol creatinine) *(Niederwieser, Curtius et al. 1982)*
The dose should be administered immediately before a meal. Sapropterin dihydrochloride should be administered in at least 2-3 daily doses in order to optimise the therapeutic response (*Belanger, Garcia et al. 2005; Blau, Fiege, et al. 2004; Blau & Burgard 2005; Wang & Yu 2006)*.

Instructions for preparation

Dissolve the tablets in a little water, orange juice or infant formula, mixing it gently. Administer the suspension within 30 minutes. Older children and adults may swallow the tablets undissolved.
Patients suffering from severe tetrahydrobiopterin deficiency may have to take Inpheno Tablets daily for life. Patients should be monitored regularly to adjust the dose to ensure normal development of the patient. The dose may have to be adjusted to take into account changes in eating habits or when a child is weaned (increased phenylalanine intake usually requires increased sapropterin dihydrochloride dosages) (Dhondt 1984; Bardelli, Donati et al. 2002). The patient's tolerance to phenylalanine may increase with increasing age and the dose must be appropriately adjusted. Body-building products and aspartame should be avoided because they contain high levels of phenylalanine which will increase the requirement for sapropterin dihydrochloride (http://en.wikipedia.org/wiki/Aspartame); (*Scheinfeld 2003; Koch and Moseley 2003*).

Table 1 Therapy of hyperphenylalaninemia *(Variation on table from Blau, Thony et al. 2001)*

Deficiency			PTPS/ **GTPCH**	**DHPR** *	**BH4-responsive PAH§**
Therapy	**Age**	**Doses /day**	**Dosage mg/kg/day**		
Sapropterin dihydrochloride monotherapy					
Sapropterin dihydrochloride	Initially	2-3	5-20	No	10-20
Combined Therapy					
Phenylalanine-low diet	Initially		No	Yes	Yes
Sapropterin dihydrochloride	Initially	2-3	2-5	**	10-20
L-DOPA + 10% carbidopa	Initially	3-4	1-3	1-3	No
	<2 years	3-4	<7	<7	No
	>2 years	3-4	8-10	8-10	No
5-Hydroxytryptophan (5HTP)	Initially	3-4	1-2	1-2	No
	<2 years	3-4	<5	<5	No
	>2 years	3-4	6-8	6-8	No

*DHPR deficiency patients are also administered 1 dose of 10-20 mg folinic acid daily given to counteract intracranial calcification *(Coskun, Ozalp et al. 1993)*.
** For CRM mutants 8-20 mg/kg/d divided in 3-4 doses
§ Tetrahydrobiopterin (BH4)-responsive PKU

Some cases of mild and transient PTPS deficiency and PCD deficiency can also be treated with sapropterin dihydrochloride monotherapy. Please note that little of the administered sapropterin can cross the blood-brain barrier *(Kapatos & Kaufman 1981)*, so in severe forms of tetrahydrobiopterin deficiency neurological damage may continue if treated with sapropterin dihydrochloride only. Treatment with neurotransmitter precursors, L-dopa and 5-hydroxytryptophan may be required in addition to sapropterin dihydrochloride therapy. See Table 1 above (combined therapy). Carbidopa, an inhibitor of peripheral aromatic amino acid decarboxylase reduces the therapeutic requirements of L-dopa. Two different preparations of L-dopa are commercially available with 10% and 25% carbidopa. Use of L- dopa/25% carbidopa as slow release preparation (Sinemet Depot) seems to be beneficial in patients with the severe form of tetrahydrobiopterin deficiency *(Blau, Thony et al. 2001)*
It is essential to have long term follow-up of urinary pterins to rule out transient defects that may persist for several months *(Matalon 1984)*. Often the symptoms of the deficiency have diurnal variations and changes in the schedule of treatment may be required *(Blau, Thony et al. 1993)*. In tetrahydrobiopterin-responsive PKU phenylalanine levels may decrease in the sapropterin dihydrochloride loading test during diagnosis but then rise even with treatment. It is essential to monitor tetrahydrobiopterin-responsive PKU patients 24 hours after diagnosis and then on a continual basis thereafter to ensure that the phenylalanine levels remain low *(Blau & Trefz 2002)*. Not all tetrahydrobiopterin responders can be successfully treated with sapropterin dihydrochloride. Those who show phenylalanine levels within the normal range over at least a week on no diet or a relaxed diet can be tried with sapropterin dihydrochloride treatment instead of the PKU diet or tried with a combination of both (relaxed diet with sapropterin dihydrochloride supplement) *(Weglage, Grenzebach et al. 2002)*.
Neurological deterioration can be prevented or at least minimised, by early treatment. Some benefit will result even if treatment starts later *(Fukuda, Tanaka et al. 1985; Blau, Ichinose et al. 1995; Dudesek, Roeschinger et al. 2001; Giewska, Bich et al. 2001; Liu, Chiang et al. 2001; Al Aqeel, Ozand et al. 1991; Blau, Thony et al. 2001)*.
If a patient forgets to take his medication, the return of neurological symptoms will most likely occur within a short period. The time of symptom reoccurrence depends on the severity of the condition. Some patients on neurotransmitter treatment have had neurological problems with phenylalanine concentrations as low as 360 micromol/l (6 mg/dl). Phenylalanine interferes with the membrane transport of neurotransmitter precursors and inhibits tyrosine and tryptophan hydroxylase *(Blau, Thony et al. 1993)*. It has also been reported that a return of cardiopulmonary problems occurred on withdrawal of treatment *(Al Aqeel, Ozand et al. 1991)*.

Use in patients with impaired renal function

There has been no testing performed in patients with impaired renal function. Biopterin (a metabolite of tetrahydrobiopterin and sapropterin) is found in increased amounts in patients with kidney disease. Caution should therefore be exercised when treating patients with impaired renal function, as administration of sapropterin dihydrochloride will increase the biopterin levels in the urine further *(Yokoyama, Tajima et al. 2002)*.

Use in patients with impaired hepatic function

There has been no testing performed in patients with impaired hepatic function.

Use in the elderly

There is no experience in treating the elderly with sapropterin dihydrochloride. Tetrahydrobiopterin is a substance found in the body of healthy individuals and is not expected to cause any complications with the elderly *(Komori, Matsuishi et al.1999)*.

Use in paediatric patients

The majority of the patients treated are children. The dosage is given in mg/kg to allow for growth.

4.3 Contraindications

Sapropterin is a nature identical substance (called tetrahydrobiopterin when endogenous) found in all organs of the body in people not suffering from its deficiency *(Komori, Matsuishi et al. 1999)*. Over sensitivity to the product is not expected when administered orally at the appropriate dose

4.4 Special warnings and special precautions for use

Vasodilating properties of sapropterin have been reported *in vitro* and *in vivo*. It has been found that sapropterin increases myocardial blood flow in healthy volunteers. The blood pressure of patients should be measured before and during therapy especially if more than 15 mg/kg is administered *(Walter, Kaufmann et al. 2001)*.

4.5 Interactions with other medicinal products and other forms of interaction

Tetrahydrobiopterin deficient patients usually require neurotransmitter precursor treatment. There is competition between phenylalanine and L-DOPA to cross the blood brain barrier. Sapropterin lowers phenylalanine levels and allows L-DOPA to be absorbed more effectively. Increasing the dose of sapropterin dihydrochloride may allow the dose of L- DOPA to be decreased *(Roze, Vidailhet et al 2006; McInnes, Kaufman et al 1984; Tanaka& Matsuo 1989)*.

Some drugs have been reported to be strong inhibitors of DHPR and this may cause adverse effects in patients with tetrahydrobiopterin deficiency. Particularly trimethoprim sulfamethoxazole (a widely used antibiotic for bacterial sinusitis, urinary tract infections and otitis media) interferes with pterin and folate metabolism. Methotrexate, another DHPR inhibitor used in the therapy of neoplasia causes impaired cerebral and biogenic amine metabolism *(Blau, Thony et al. 2001)*.

4.6 Pregnancy and lactation

Pregnancy

Data on a limited number (four) of exposed pregnancies indicate no adverse effects of sapropterin on pregnancy or on the health of the foetus/newborn child *(Giewska, Bich et al. 2001; Niederwieser, Shintaku et al. 1986)*. To date no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development *(Sawada, Shintaku et al. 1986)*.

Women of child-bearing potential

Caution should be exercised when prescribing to pregnant women.
For tetrahydrobiopterin deficient patients the question of pregnancy will be more influenced by genetic questions and the need to continue with neurotransmitter precursor treatment. This treatment is difficult to adjust even without pregnancy, and the effects on the foetus have yet to be determined. It is likely that only patients being treated with monotherapy could have the possibility of being treated with sapropterin dihydrochloride during pregnancy.

Lactation

Endogenous tetrahydrobiopterin can be found in breast milk of healthy individuals. There is insufficient information on the excretion of sapropterin dihydrochloride in human or animal breast milk. A risk to the suckling child cannot be excluded. A decision on whether to continue/discontinue therapy with sapropterin dihydrochloride should be made taking into account the benefit of breast-feeding to the child and the benefit of sapropterin therapy to the woman. It is also essential to determine if the child is itself suffering from tetrahydrobiopterin deficiency or tetrahydrobiopterin responsive PKU. In this situa-tion the child may benefit from the decreased phenylalanine levels of breast milk and additional sapropterin available from its mother (*Dhondt 1984; Bardelli, Donati et al. 2002*).

4.7 Effects on ability to drive and use machines

No studies on the ability to drive or use machines while being treated with sapropterin have been performed.

4.8 Undesirable effects

We have not performed any organized clinical trials with sapropterin dihydrochloride. According to literature reference, an unapproved sapropterin product had been provided to be administered to patients suffering from tetrahydrobiopterin deficiency since the unapproved sapropterin product to doctors using tetrahydrobiopterin tablets in Germany up to 1998 reported one child on 2.5-10 mg/kg/d who experienced a transient rush. There have been no other reports from the doctors or patients indicating any undesirable effects. Neurotransmitter precursors, are administered to many of the patients. Insomnia and choreoathetoid movements appeared as side effects of the neurotransmitter precursors. It may be difficult to distinguish which drug is responsible for the adverse reactions.
Carbidopa, which is also administered, is known to show toxic effects *(Niederwieser, Blau et al. 1984)*.
Often the symptoms of the deficiency have diurnal and between-days variation.
The safety of a similar sapropterin product was reported in a Japanese publication.
A double blind clinical trial using sapropterin dihydrochloride and placebo was performed on 84 autistic patients in 4 clinics in Japan. A dosage of 1-3 mg/kg/day was administered to half of the cases and the other half were given a placebo. The study was for 12 weeks following a washout period of at least a week. No adverse reaction was observed in the double blind trial or the open trials (long term treatment of patients with atypical phenylketonuria (tetrahydrobiopterin deficiency)) *(Naruse, Hayashi et al. 1987)*.
But the same sapropterin product's packaging leaflet states that the overall incidence of adverse reactions in 318 patients enrolled in clinical trials of this sapropterin product was 21.4% (63/318). Major symptoms were psychoneurotic (sleep disorders) in 13.8% (44/318), urological (e.g., pollakisuria) in 9.1% (29/318) and gastrointestinal (e.g., loose bowels) in 2.8% (9/318).1/16 patients experienced an increase in convulsion rate.
Tetrahydrobiopterin tablets have been used in clinical trials for many other illnesses and to date no adverse effects have been reported *(Walter, Kaufmann et al. 2001; Haan 1990)*

4.9 Overdose

No case of overdose has been reported to date.

5. PHARMACOLOGICAL PROPERTIES

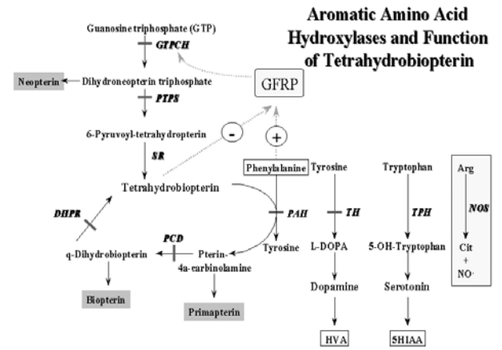
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Various alimentary tract and metabolism products

Mechanism of action of tetrahydrobiopterin

Endogenous mean total serum biopterin derivative levels in healthy adult males and females were 1.75 µg/l and 1.53 µg/l, respectively, increased with age and followed a cyclic pattern during menstruation. Differentiation of the different biopterin derivatives shows that tetrahydrobiopterin levels decrease with age as dihydrobiopterin and biopterin increase.
Wide distribution in adult tissues and variation in concentration independent of serum levels demonstrated local synthesis *(Leeming & Blair 1980)*.
The best established function of tetrahydrobiopterin in man is as the natural cofactor for phenylalanine-4-hydroxylase (PAH), tyrosine-3-hydroxylase, and tryptophan-5- hydroxylase.The latter two are key enzymes in the biosynthesis of biogenic amines (dopamine and serotonin). In addition to the hydroxylation of aromatic amino acids, tetrahydrobiopterin serves as a cofactor for nitric oxide synthase and glyceryl-ether monooxygenase.
In a normally functioning body tetrahydrobiopterin is produced naturally, but some children are born with insufficient amounts of tetrahydrobiopterin (tetrahydrobiopterin deficient).
This deficiency can result from any of four enzyme deficiencies, i.e.
GTP cyclohydrolase 1 (GTPCH),
6-Pyruvoyltetrahydropterin synthase (PTPS),
Pterin-4a-carbinolamine dehydratase (PCD) or
Dihydropteridine reductase (DHPR) *(Blau, Thony et al. 2001)*.
Classic PKU, in contrast, results from a deficiency in phenylalanine hydroxylase.
In some PKU patients it was found that the phenylalanine hydroxylase enzyme responds to increased sapropterin. Those who respond were found to have residual phenylalanine hydroxylase activity (20-30%). The sapropterin either increases the gene expression for the enzyme or allows the low affinity of the enzyme for tetrahydrobiopterin to be compensated for by higher concentrations of the cofactor *(Spaapen, Bakker et al. 2001)*.

Figure 1: *Tetrahydrobiopterin metabolism and the enzymes implicated in tetrahydrobiopterin deficiencies.*



Pharmacodynamic effects

Sapropterin reduces the phenylalanine levels in the serum of patients suffering from tetrahydrobiopterin deficiency. This decrease is substantial in PTPS and GTPCH deficiency (approx. 90% in 8 hours). The decrease in DHPR deficiency is slower (approx. 60% in 8 hours) for the same dosage.
In tetrahydrobiopterin-responsive PKU phenylalanine levels decrease slowly and may rise again slowly later despite treatment *(Weglage, Grenzebach et al. 2002)*.
The degree to which the phenylalanine levels are reduced in tetrahydrobiopterin deficiency patients upon administration of sapropterin dihydrochloride is dependent on the dose and the severity of the deficiency and the enzyme affected) *(Blau, Thony et al. 1993)*. The degree to which the phenylalanine levels are reduced in PKU patients depends on a variety of factors but particularly the mutation causing the PKU and the residual activity of the PAH enzyme.
Higher doses of sapropterin dihydrochloride (10-20 mg/kg) are required to reduce the phenylalanine levels of DHPR defi-ciency and PKU patients compared to PTPS deficient patients (1-10 mg/kg) *(Blau, Thony et al. 2001)*.
The phenylalanine values once decreased may remain low for up to two days in tetrahydrobiopterin deficient patients *(Curtius, Niederwieser et al. 1979; Beck, Christensen et al. 1983)*. Daily administration of sapropterin dihydrochloride keeps the phenylalanine levels in the normal healthy range. Careful monitoring is essential *(Niederwieser, Matasovic et al. 1982; Blau, Thony et al. 2001)*.
In loading tests with sapropterin dihydrochloride, tyrosine levels rise as the phenylalanine levels fall, as is the case in normal healthy persons. The increase occurs rapidly and the effect is short lived (*Ponzone Ferraris 2006; Wang & Yu 2006)*. The increase depends on the remaining tyrosine hydroxylase activity of the patient *(Niederwieser, Blau et al. 1984)*.
The cofactor tetrahydrobiopterin allows the enzymes to play their role in the conversion of phenylalanine to tyrosine which in turn leads to an increase in HVA from dopamine and HIAA from serotonin *(Blau, Thony et al. 1993)*.
The increase in the cerebrospinal fluid (CSF) metabolites is limited because sapropterin crosses the blood brain barrier in very small amounts *(Kapatos & Kaufman 1981; Blau, Ichinose et al. 1995; Niederwieser, Blau et al. 1984; Ponzone Ferraris 2006)*.
Although tetrahydrobiopterin deficient persons exhibit a higher dietary phenylalanine tolerance than classical PKU patients, a limiting factor in the response to neurotransmitter precursor therapy might be the plasma phenylalanine fluctuations which could alter the dose-effect relationships of these substances by interfering with their membrane transport or by competitive inhibition of tyrosine and tryptophan hydroxylase. The control of blood phenylalanine has to be stricter than in other HPA's. Some patients on neurotransmitter treatment have had neurological problems with phenylalanine concentrations as low as 360 µmol/l (6 mg/dl) *(Blau, Thony et al. 1993)*.

Clinical efficacy

Tetrahydrobiopterin deficiency

The evidence of the therapeutic effects of sapropterin dihydrochloride is based on over 25 years of treatment of at least 250 tetrahydrobiopterin deficient patients worldwide.

If diagnosis and treatment are during the neonatal phase of life then mental retardation can be avoided unless neurological damage has occurred during pregnancy. If treatment begins after the age of 2-4 months, when clinical symptoms of the deficiency become apparent, then mental retardation will usually remain despite treatment *(Fukuda, Tanaka et al. 1985; Blau, Ichinose et al. 1995; Dudesek, Roeschingeret al. 2001; Giewska, Bich et al. 2001; Liu, Chiang et al. 2001)*. But other symptoms such as dystonic movements, convulsions, intention tremors and fits should slowly disappear with treatment. Muscle tone and head control improve. The horizontal nystagmus and fever attacks disappear. Sebaceous skin becomes normaland the hair becomes darker. However, concentrations of HVA and HIAA often remainlow in the CSF so therapy with neurotransmitter precursors and decarboxylase inhibitor is required in addition to sapropterin dihydrochloride *(Blau, Ichinose et al. 1995)*. In some patients monotherapy with sapropterin dihydrochloride is sufficient to see improvements in their physical and mental condition *(Niederwieser, Blau et al. 1984; Dudesek, Roeschinger et al. 2001; Niederwieser, Matasovic et al. 1982; Blau, Thony et al. 2001)*.

Although some tetrahydrobiopterin deficient patients diagnosed late do not recover as well as those diagnosed earlier, good improvements are seen. By 1993, of the 250 patients diagnosed, 2 PTPS and 6 DHPR deficient patients had died although treatment had been started within the first month of life. These deaths are probably due to a number of reasons:

a) Fetal brain damage in PTPS deficiency: low birth weight, clinical signs are often reported.

b) Possible iatrogenic damage of neurotransmitter precursors.

c) The quality of response depends on the severity of the metabolic defect. Better response is found with patients who have near normal CSF HVA concentrations at diagnosis. In DHPR deficiency, it has been also suggested that CRM mutants may have a better prognosis *(Blau, Thony et al. 1993)*.

The mortality rate is higher among DHPR deficiency patients than among PTPS patients *(Blau, Thony et al. 2001)*.

BH4 responsive PKU

There is a varying degree of success in the treatment of BH4 responsive patients. Some may be treated with sapropterin monotherapy without diet but most continue to follow at least a mild diet in addition to sapropterin therapy *(Belanger, Garcia et al. 2005; Blau, Fiege et al. 2003; Cerone, Schiaffino et al. 2004; Hennerman, Buhrer et al. 2005; Koch, Guttler 2002; Lambruschini, Perez et al. 2005; Mitchell, Wilcken et al. 2005; Shintaku, Kure et al. 2004; Spaapen, Rubio et al. 2003; Steinfeld, Kohlschutter et al. 2004; Trefz, Scheible et al. 2005)*.

5.2 Pharmacokinetic properties

Tetrahydrobiopterin is endogenous in the body of healthy individuals. The distribution, absorption and excretion depend on the functional requirements of the body. The body of the healthy person has processes that allow tetrahydrobiopterin to be used optimally and excretes the breakdown products that are not required.

Sapropterin dihydrochloride has been found in non-clinical studies to be absorbed into the same tissues as endogenous tetrahydrobiopterin so that the natural processes can continue undisturbed.

Cmax and the AUC at 10 hours were similar for all individuals for the same dose. Cmax ranged between 258.7 to 295.0 nmol/l for 10 mg/kg of administered sapropterin dihydrochloride.

The AUC 0-∞ ranged from 2959 to 3159 nmol·h/l for 10 mg/kg and was similar to 3603 nmol·h/l found for 20 mg/kg *(Fiege & Ballhausen 2004)*.

Absorption/Distribution

It was found that most of the ingested sapropterin dihydrochloride is absorbed in the gastrointestinal tract *(Niederwieser, Matasovic et al. 1986)*.

Sapropterin is rapidly absorbed mainly in the duodenum and the jejunum and less in the stomach. Absorption is more rapid in newborns than in older patients.

As the dose increases the Tmax and T½ decreases slightly. Since the individual differences in Tmax and T½ are bigger than the differences caused by dose, this difference is not considered significant. In most publications regardless of dose the half-life in serum is about 3.5 hours (range 3.3- 5.1) *(Fiege & Ballhausen 2004)*. In red blood cells the half-life of sapropterin is 15 h. Tmax is usually about 4 hours regardless of whether the person is healthy or is suffering from PKU or HPA.

As the half-life of sapropterin is only approximately 3.5 h and that of phenylalanine is 20- 30 h, patients should have their doses divided over the day *(Ponzone, Guardamagna 1993; Blau Burgard 2005; Belanger, Garcia et al. 2005)*.

Nonclinical studies in mice showed that sapropterin is taken up from the blood primarily into the liver and kidney. In pregnant mice, the sapropterin passed through the placenta and was distributed uniformly in the fetal tissues. The developmental increase in hepatic tetrahydrobiopterin accumulation was correlated with those of the activities of phenylalanine hydroxylase and GTP cyclohydrolase I, the rate-limiting enzyme of the tetrahydrobiopterin biosynthetic pathway *(Hoshiga, Hatakeyama et al. 1993)*.

Metabolism/Elimination

Sapropterin (tetrahydrobiopterin) is converted to dihydrobiopterin and biopterin in the blood. Dihydrobiopterin is reconverted to tetrahydrobiopterin. Tetrahydrobiopterin is further converted to pterin, isoxanthopterin, 6-hydroxylumazine, sepialumazine, 2'-deoxy-sepialumazine, sepiapterin and 2'-deoxysepiapterin and excreted in the urine and faeces *(Niederwieser, Matasovic et al. 1986)*. Only a minor part of the ingested sapropterin dihydrochloride is excreted in urine and faeces as pterins and lumazines (<10 mol%).

Within 4 hours most of the sapropterin dihydrochloride metabolites had been excreted in the urine in the form of pterins and lumazines. The remainder was excreted in the faeces between 24 - 48 hours *(Niederwieser, Matasovic et al. 1986)*. Biopterin, a fully oxidized form of tetrahydrobiopterin, was not accumulated in any tissues and was excreted rapidly in the urine within four hours and later in the faeces (*Fiege & Ballhausen 2004)*.

The terminal half-life is usually around 8 hours. Most of the ingested sapropterin is used as a cofactor (mainly for PAH in the liver). The apparent clearance was estimated to be 900 l/h (*Fiege & Ballhausen 2004)*.

5.3 Preclinical safety data

A preclinical testing have been performed on rats to study the effect of sapropterin dihydrochloride on the pregnant female and the development of the foetus. No adverse effects occurred. The NOAEL (no observed adverse effects level) was established at the dose of 1000 mg/kg body weight.

Please note that the data from the animal testing below was collected from the literature and was not performed with the 99.5% pure sapropterin dihydrochloride.

A review of the preclinical literature reveal no special hazard to humans based on conventional studies of safety pharmacology, repeated dose toxicity, acute toxicity, genotoxicity and reproduction toxicity. Vomiting was seen in studies with dogs *(Hirotsu, Nakamura et al. 1990; Naruse, Hayashi et al. 1987)*.

Oral administration of 1318 mg/kg to mice yielded no signs of morbidity or mortality nor did the subchronic 92-day administration of 10 mg and 50 mg/kg sapropterin dihydrochloride *(Lewandowski, Combs et al. 1986)*.

An LD50 of 260 mg/kg was determined in a 14-day intraperitoneal survival study. Sapropterin dihydrochloride (300 mg/kg) administered subcutaneously caused two out of twelve mice to die *(Lewandowski, Combs et al. 1986)*.

The higher toxicity found in subcutaneous and intraperitoneal administration may be because of the acidity of sapropterin dihydrochloride. A 1 mM solution of sapropterin dihydrochloride in water gives a pH of 3.0 and a 1 M solution of sapropterin dihydrochloride in water gives a pH of 0.45. This toxic effect could be avoided by ensuring that the blood buffering capacity is not exceeded.

No carcinogenic or genotoxic studies have been performed.

6. PHARMACEUTICAL PARTICULARS

Please see the Tetrahydrobiopterin website, which provides detailed information on tetrahydrobiopterin deficiencies and BH4 responsive PKU and their treatment.

6.1 List of excipients

Ascorbic acid
Microcrystalline cellulose
Mannitol
Crospovidone
Magnesium stearate
Coloring agents

6.2 Incompatibility

Not applicable.

6.3 Shelf life

2 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 the container

High-density polyethylene (HDPE) bottle.
Each bottle contains a desiccant (silica gel). 1 bottle per carton.

6.6 Special precautions for disposal

No special precautions are required in the handling of this product.

6.7 Manufacturer

Synmosa Biopharma Corporation, Synmosa Plant
No. 6, Kuang Yeh 1st Road, Hu-Kuo Hsiang, Hsin-Chu Ind. Park, Hsin Chu Hsien, Taiwan, R.O.C.

6.8 MARKETING AUTHORISATION HOLDER

InnoPharmax, Inc.
9F., No. 22, Lane 478, Rueiguang Rd.
Neihu District, Taipei
Taiwan, R.O.C.

7. MARKETING AUTHORISATION NUMBER

MOHW-PM-058052

8. DATE OF REVISION OF THE TEXT

Date of revision of the text: 10/2015.

LITERATURE

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