SAPROPTERIN DIHYDROCHLORIDE- sapropterin dihydrochloride tablet
Par Pharmaceutical, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SAPROPTERIN DIHYDROCHLORIDE TABLETS safely and effectively. See full prescribing information for SAPROPTERIN DIHYDROCHLORIDE TABLETS.

SAPROPTERIN DIHYDROCHLORIDE tablets, for oral use
Initial U.S. Approval: 2007

INDICATIONS AND USAGE
Sapropterin dihydrochloride tablets are a phenylalanine hydroxylase activator indicated to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin-(BH4-) responsive Phenylketonuria (PKU). Sapropterin dihydrochloride tablets are to be used in conjunction with a Phe-restricted diet. (1)

DOSAGE AND ADMINISTRATION
All patients with PKU who are being treated with sapropterin dihydrochloride tablets should also be treated with a Phe-restricted diet. (2.1)

Starting Dosage (2)
- Patients 1 month to 6 years: The recommended starting dose of sapropterin dihydrochloride tablets is 10 mg/kg taken once daily. (2.1)
- Patients 7 years and older: The recommended starting dose of sapropterin dihydrochloride tablets is 10 to 20 mg/kg taken once daily. (2.1)

Dosage Adjustment (2)
- Doses of sapropterin dihydrochloride tablets may be adjusted in the range of 5 to 20 mg/kg taken once daily. Monitor blood Phe regularly. (2.1, 5.4)

Preparation and Administration (2)
- Take with a meal. (2.2)
- Swallow tablets whole or after mixing in a small amount of soft foods or dissolving in recommended liquid. Swallow oral solution after mixing powder in a small amount of soft foods or dissolving in recommended liquids. See full prescribing information for complete information on mixing with food or liquid. (2.2)

DOSAGE FORMS AND STRENGTHS
- Tablets: 100 mg sapropterin dihydrochloride. (3)

CONTRAINDICATIONS
None. (4)

WARNINGS AND PRECAUTIONS
- Hypersensitivity reactions including anaphylaxis have occurred. (5.1)
- Gastritis was reported in clinical trials. Monitor patients for signs of gastritis. (5.2)
- Children younger than 7 years treated with sapropterin dihydrochloride doses of 20 mg/kg per day are at increased risk for low levels of blood Phe compared with children 7 years and older. (5.3)
- Monitor blood Phe levels during treatment to ensure adequate blood Phe control. (5.4)
- Identify non-responders to sapropterin dihydrochloride treatment:
  Not all patients with PKU respond to treatment with sapropterin dihydrochloride. (5.5)
- Interaction with levodopa reported postmarketing causing convulsions, over-stimulation or irritability; monitor patients for a change in neurologic status. (5.6, 7)
- There have been post-marketing reports of hyperactivity with administration of sapropterin dihydrochloride. Monitor patients for hyperactivity. (5.7)

ADVERSE REACTIONS
Most common adverse reactions (≥4%) are: headache, rhinorrhea, pharyngolaryngeal pain, diarrhea, vomiting, cough, and nasal congestion. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical at 1-800-828-9393, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
- Inhibitors of Folate Metabolism (e.g., methotrexate): Can decrease endogenous BH4 levels; frequently monitor blood Phe levels. (7)
- Drugs Affecting Nitric Oxide-Mediated VASORELAXATION (e.g., PDE-5 inhibitors): Potential for vasorelaxation; monitor blood pressure. (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.
FULL PRESCRIBING INFORMATION: CONTENTS*
1 INDICATIONS AND USAGE
Sapropterin dihydrochloride tablets are indicated to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4-) responsive Phenylketonuria (PKU). Sapropterin dihydrochloride tablets are to be used in conjunction with a Phe-restricted diet.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
Sapropterin dihydrochloride tablets are indicated to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4-) responsive Phenylketonuria (PKU). Sapropterin dihydrochloride tablets are to be used in conjunction with a Phe-restricted diet.
2 DOSAGE AND ADMINISTRATION

2.1 Dosage

Treatment with sapropterin dihydrochloride tablets should be directed by physicians knowledgeable in the management of PKU.

All patients with PKU who are being treated with sapropterin dihydrochloride tablets should also be treated with a Phe restricted diet.

Starting Dosage

Patients 1 month to 6 years: The recommended starting dose of sapropterin dihydrochloride tablets is 10 mg/kg taken once daily.

Patients 7 years and older: The recommended starting dose of sapropterin dihydrochloride tablets is 10 to 20 mg/kg taken once daily.

Dosage Adjustment

If a 10 mg/kg per day starting dose is used, then response to therapy is determined by change in blood Phe following treatment with sapropterin dihydrochloride tablets at 10 mg/kg per day for a period of up to 1 month. Blood Phe levels should be checked after 1 week of sapropterin dihydrochloride treatment and periodically for up to a month. If blood Phe does not decrease from baseline at 10 mg/kg per day, the dose may be increased to 20 mg/kg per day. Patients whose blood Phe does not decrease after 1 month of treatment at 20 mg/kg per day are non-responders and treatment with sapropterin dihydrochloride tablets should be discontinued in these patients.

If a 20 mg/kg per day starting dose is used, then response to therapy is determined by change in blood Phe following treatment with sapropterin dihydrochloride tablets at 20 mg/kg per day for a period of 1 month. Blood Phe levels should be checked after 1 week of sapropterin dihydrochloride treatment and periodically during the first month. Treatment should be discontinued in patients who do not respond to sapropterin dihydrochloride tablets.

Once responsiveness to sapropterin dihydrochloride tablets has been established, the dosage may be adjusted within the range of 5 to 20 mg/kg per day according to response to therapy. Periodic blood Phe monitoring is recommended to assess blood Phe control [see Warnings and Precautions (5.3)].

2.2 Preparation and Administration Instructions

Take Sapropterin dihydrochloride tablets orally with a meal to increase absorption, preferably at the same time each day. A missed dose should be taken as soon as possible, but two doses should not be taken on the same day.

Sapropterin Dihydrochloride Tablets

Sapropterin dihydrochloride tablets may be swallowed either as whole tablets or dissolved in 120 to 240 mL of water or apple juice and taken orally within 15 minutes of dissolution. It may take a few minutes for the tablets to dissolve. To make the tablets dissolve faster, tablets may be stirred or crushed. The tablets may not dissolve completely. Patients may see small pieces floating on top of the water or apple juice. This is normal and safe for patients to swallow. If after drinking the medicine patients still see pieces of the tablet in the container, more water or apple juice can be added to make sure all of the medicine is consumed. Sapropterin dihydrochloride tablets may also be crushed and then mixed in a small amount of soft foods such as apple sauce or pudding.

3 DOSAGE FORMS AND STRENGTHS

Sapropterin dihydrochloride tablets are for oral use. Each tablet contains 100 mg of sapropterin dihydrochloride (equivalent to 76.8 mg of sapropterin base). Tablets are off-white to light yellow, mottled, uncoated, round shaped tablets debossed with ‘P’ on one side and ‘720’ on other side.

4 CONTRAINDICATIONS

None.
5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions Including Anaphylaxis
Sapropterin dihydrochloride is not recommended in patients with a history of anaphylaxis to sapropterin dihydrochloride. Hypersensitivity reactions, including anaphylaxis and rash, have occurred [see Adverse Reactions (6.2)]. Signs of anaphylaxis include wheezing, dyspnea, coughing, hypotension, flushing, nausea, and rash.

Discontinue treatment with sapropterin dihydrochloride in patients who experience anaphylaxis and initiate appropriate medical treatment. Continue dietary Phe restrictions in patients who experience anaphylaxis.

5.2 Gastritis
During clinical studies, gastritis was reported as a serious adverse reaction. Monitor patients for signs and symptoms of gastritis.

5.3 Hypophenylalaninemia
In clinical trials, some patients have experienced low blood Phe levels. Children younger than 7 years treated with sapropterin dihydrochloride doses of 20 mg/kg per day are at increased risk for low levels of blood Phe compared with patients 7 years and older [see Adverse Reactions (6.1)].

5.4 Monitor Blood Phe Levels During Treatment
Prolonged elevations in blood Phe levels in patients with PKU can result in severe neurologic damage, including severe mental retardation, microcephaly, delayed speech, seizures, and behavioral abnormalities. Conversely, prolonged levels of blood Phe that are too low have been associated with catabolism and protein breakdown. Active management of dietary Phe intake while taking sapropterin dihydrochloride is required to ensure adequate Phe control and nutritional balance. Monitor blood Phe levels during treatment to ensure adequate blood Phe level control. Frequent blood monitoring is recommended in the pediatric population [see Dosage and Administration (2.1)].

5.5 Identify Non-Responders to Sapropterin Dihydrochloride Treatment
Not all patients with PKU respond to treatment with sapropterin dihydrochloride. In two clinical trials at a dose of 20 mg/kg per day, 56% to 75% of pediatric PKU patients responded to treatment with sapropterin dihydrochloride, and in one clinical trial at a dose of 10 mg/kg per day, 20% of adult and pediatric PKU patients responded to treatment with sapropterin dihydrochloride [see Clinical Studies (14)].

Response to treatment cannot be pre-determined by laboratory testing (e.g., molecular testing), and can only be determined by a therapeutic trial of sapropterin dihydrochloride [see Dosage and Administration (2.1)].

5.6 Interaction with Levodopa
In a 10-year post-marketing safety surveillance program for a non-PKU indication using another formulation of the same active ingredient (sapropterin), 3 patients with underlying neurologic disorders experienced convulsions, exacerbation of convulsions, over-stimulation, or irritability during co-administration of levodopa and sapropterin. Monitor patients who are receiving levodopa for change in neurologic status during treatment with sapropterin dihydrochloride [see Drug Interactions (7)].

5.7 Hyperactivity
In the post-marketing safety surveillance program for PKU, 2 patients experienced hyperactivity with administration of sapropterin dihydrochloride. Monitor patients for hyperactivity.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

PKU Clinical Studies

The safety of sapropterin dihydrochloride was evaluated in 7 clinical studies in patients with PKU (aged 1 month to 50 years) [see Clinical Studies (14)].

In Studies 1-4 (controlled and uncontrolled studies), 579 patients with PKU aged 4 to 49 years received sapropterin dihydrochloride in doses ranging from 5 to 20 mg/kg per day for lengths of treatment ranging from 1 to 164 weeks. The patient population was evenly distributed in gender, and approximately 95% of patients were Caucasian. The most common adverse reactions (≥4% of patients) were headache, rhinorrhea, pharyngolaryngeal pain, diarrhea, vomiting, cough, and nasal congestion.

The data described in Table 3 reflect exposure of 74 patients with PKU to sapropterin dihydrochloride at doses of 10 to 20 mg/kg per day for 6 to 10 weeks in two double-blind, placebo-controlled clinical trials (Studies 2 and 4).

Table 3 enumerates adverse reactions occurring in at least 4% of patients treated with sapropterin dihydrochloride in the double-blind, placebo-controlled clinical trials described above.

Table 3: Summary of Adverse Reactions Occurring in ≥4% of Patients in Placebo-Controlled Clinical Studies with Sapropterin Dihydrochloride

<table>
<thead>
<tr>
<th>MedDRA Preferred Term</th>
<th>Treatment Sapropterin Dihydrochloride (N=74)</th>
<th>Placebo (N=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Patients (%)</td>
<td>No. Patients (%)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (15)</td>
<td>8 (14)</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>8 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Pharyngolaryngeal pain</td>
<td>7 (10)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (8)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (8)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Cough</td>
<td>5 (7)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>3 (4)</td>
<td>0</td>
</tr>
</tbody>
</table>

In open-label, uncontrolled clinical trials (Studies 1 and 3) all patients received sapropterin dihydrochloride in doses of 5 to 20 mg/kg per day, and adverse reactions were similar in type and frequency to those reported in the double-blind, placebo-controlled clinical trials [see Clinical Studies (14)].

In Study 5, 65 pediatric patients with PKU aged 1 month to 6 years received sapropterin dihydrochloride 20 mg/kg per day for 6 months. Adverse reactions in these patients were similar in frequency and type as those seen in other sapropterin dihydrochloride clinical trials except for an increased incidence of low Phe levels.

Twenty-five percent (16 out of 65) of patients developed Phe levels below normal for age [see Warnings and Precautions (5.3), Pediatric Use (8.4), and Clinical Studies (14)].

In Study 6, a long-term, open-label, extension study of 111 patients aged 4 to 50 years, receiving Sapropterin dihydrochloride in doses ranging from 5 to 20 mg/kg per day, adverse reactions were similar in type and frequency to those reported in the previous clinical studies. Fifty-five patients received Sapropterin dihydrochloride both as dissolved and intact tablets. There were no notable differences in the incidence or severity of adverse reactions between the two methods of administration. The mean (± SD) exposure to sapropterin for the entire study population was 659 ± 221 days (maximum 953 days).

In Study 7, 27 pediatric patients with PKU aged 0 to 4 years received sapropterin dihydrochloride 10
mg/kg per day or 20 mg/kg per day. Adverse reactions were similar in type and frequency to those observed in other clinical trials, with the addition of rhinitis, which was reported in 2 subjects (7.4%).

Safety Experience from Clinical Studies for Non-PKU Indications

Approximately 800 healthy volunteers and patients with disorders other than PKU, some of whom had underlying neurologic disorders or cardiovascular disease, have been administered a different formulation of the same active ingredient (sapropterin) in approximately 19 controlled and uncontrolled clinical trials. In these clinical trials, subjects were administered sapropterin at doses ranging from 1 to 100 mg/kg per day for lengths of exposure from 1 day to 2 years.

Serious and severe adverse reactions (regardless of causality) during sapropterin administration were convulsions, exacerbation of convulsions [see Warnings and Precautions (5.6)], dizziness, gastrointestinal bleeding, post-procedural bleeding, headache, irritability, myocardial infarction, overstimulation, and respiratory failure. Common adverse reactions were headache, peripheral edema, arthralgia, polyuria, agitation, dizziness, nausea, pharyngitis, abdominal pain, upper abdominal pain, and upper respiratory tract infection.

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of sapropterin dihydrochloride. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish causal relationship to drug exposure.

In worldwide marketing experience, the most common adverse reactions due to sapropterin dihydrochloride are oropharyngeal pain, pharyngitis, esophageal pain, gastritis, dyspepsia, abdominal pain, nausea and vomiting. Hypersensitivity reactions including anaphylaxis and rash have been reported. Most hypersensitivity reactions occurred within several days of initiating treatment. Two cases of hyperactivity have been reported, including one case in a patient who received an accidental overdose of sapropterin dihydrochloride [see Warnings and Precautions (5.1, 5.7)].

7 DRUG INTERACTIONS

Table 4 includes drugs with clinically important drug interactions when administered with sapropterin dihydrochloride and instructions for preventing or managing them.

<table>
<thead>
<tr>
<th>Levodopa</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Impact</strong></td>
<td>Sapropterin dihydrochloride may increase the availability of tyrosine, a precursor of levodopa. Neurologic events were reported post-marketing in patients receiving sapropterin and levodopa concomitantly for a non-PKU indication [see Warnings and Precautions (5.6)]</td>
<td></td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Monitor patients for a change in neurologic status.</td>
<td></td>
</tr>
</tbody>
</table>

Inhibitors of Folate Metabolism (e.g., methotrexate)

| Clinical Impact | Inhibitors of folate metabolism can decrease endogenous BH4 levels by inhibiting the enzyme dihydropteridine reductase (DHPR), which is involved in the in vivo metabolism and recycling of sapropterin. | | |
| **Intervention** | Frequently monitor blood Phe levels. | | |

Drugs Affecting Nitric Oxide-Mediated Vasorelaxation (e.g., PDE-5 inhibitors such as sildenafil, vardenafil, or tadalafil)

| Clinical Impact | Both sapropterin dihydrochloride and PDE-5 inhibitors may induce vasorelaxation. A reduction in blood pressure could occur; however, the combined use of these medications has not been evaluated in humans. | | |
| **Intervention** | Monitor blood pressure. | | |
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with sapropterin dihydrochloride in pregnant women. An embryo-fetal development study with sapropterin dihydrochloride in rats using oral doses up to 3 times the maximum recommended human dose (MRHD) given during the period of organogenesis showed no effects. In a rabbit study using oral administration of sapropterin dihydrochloride during the period of organogenesis, a rare defect, holoprosencephaly, was noted at 10 times the MRHD. Sapropterin dihydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Disease-associated maternal and/or embryofetal risk

Available data from the Maternal Phenylketonuria Collaborative Study on 468 pregnancies and 331 live births in PKU-affected women demonstrated that uncontrolled Phe levels above 600 micromol/L are associated with a very high incidence of neurological, cardiac, facial dysmorphism, and growth anomalies. Good dietary control of Phe levels during pregnancy is essential to reduce the incidence of Phe-induced teratogenic effects.

Animal Data

No effects on embryo-fetal development were observed in a reproduction study in rats using oral doses of up to 400 mg/kg per day sapropterin dihydrochloride (about 3 times the MRHD of 20 mg/kg per day, based on body surface area) administered during the period of organogenesis. However, in a rabbit reproduction study, oral administration of a maximum dose of 600 mg/kg per day (about 10 times the MRHD, based on body surface area) during the period of organogenesis was associated with a non-statistically significant increase in the incidence of holoprosencephaly in two high dose-treated litters (4 fetuses), compared to one control-treated litter (1 fetus).

8.3 Nursing Mothers

It is not known whether sapropterin dihydrochloride is present in human milk. Sapropterin is present in the milk of intravenously, but not orally, treated lactating rats. The developmental and health benefits of human milk feeding should be considered along with the mother’s clinical need for sapropterin dihydrochloride and any potential adverse effects on the human milk-fed child from the drug or from the underlying maternal condition. Exercise caution when sapropterin dihydrochloride is administered to a nursing woman.

8.4 Pediatric Use

Pediatric patients with PKU, ages 1 month to 16 years, have been treated with sapropterin dihydrochloride in clinical trials [see Clinical Studies (14)].

The efficacy and safety of sapropterin dihydrochloride have not been established in neonates. The safety of sapropterin dihydrochloride has been established in children younger than 4 years in trials of 6 months duration and in children 4 years and older in trials of up to 3 years in length [see Adverse Reactions (6.1)].

In children aged 1 month and older, the efficacy of sapropterin dihydrochloride has been demonstrated in trials of 6 weeks or less in duration [see Clinical Studies (14)].

In a multicenter, open-label, single arm study, 57 patients aged 1 month to 6 years who were defined as sapropterin dihydrochloride responders after 4 weeks of sapropterin dihydrochloride treatment and Phe dietary restriction were treated for 6 months with sapropterin dihydrochloride at 20 mg/kg per day. The effectiveness of sapropterin dihydrochloride alone on reduction of blood Phe levels beyond 4 weeks...
could not be determined due to concurrent changes in dietary Phe intake during the study. Mean (±SD) blood Phe values over time for patients aged 1 month to <2 years and 2 to <7 years are shown in Figure 1.

Figure 1: Mean Blood Phe Level Over Time by Age (years) (N=57)

*Error bars indicate 95% confidence interval.

8.5 Geriatric Use
Clinical studies of sapropterin dihydrochloride in patients with PKU did not include patients aged 65 years and older. It is not known whether these patients respond differently than younger patients.

10 OVERDOSAGE
Two unintentional overdosages with sapropterin dihydrochloride have been reported. One adult patient in a sapropterin dihydrochloride clinical trial received a single sapropterin dihydrochloride dose of 4,500 mg (36 mg/kg) instead of 2,600 mg (20 mg/kg). The patient reported mild headache and mild dizziness immediately after taking the dose; both symptoms resolved within 1 hour with no treatment intervention. There were no associated laboratory test abnormalities. The patient suspended therapy for 24 hours and then restarted sapropterin dihydrochloride with no reports of abnormal signs or symptoms.

In postmarketing, one pediatric patient received sapropterin dihydrochloride doses of 45 mg/kg per day instead of 20 mg/kg per day. The patient reported hyperactivity that began at an unspecified time after overdose and resolved after the sapropterin dihydrochloride dose was reduced to 20 mg/kg per day.

In a clinical study to evaluate the effects of sapropterin dihydrochloride on cardiac repolarization, a single supra-therapeutic dose of 100 mg/kg (5 times the maximum recommended dose) was administered to 54 healthy adults. No serious adverse reactions were reported during the study. The only adverse reactions reported in more than 1 subject who received the supra-therapeutic dose were
upper abdominal pain (6%) and dizziness (4%). A dose-dependent shortening of the QT interval was observed [see Clinical Pharmacology (12.2)].

Patients should be advised to notify their physicians in cases of overdose.

11 DESCRIPTION

Sapropterin dihydrochloride tablets is an orally administered Phenylalanine Hydroxylase activator (or PAH activator). Sapropterin dihydrochloride, the active pharmaceutical ingredient in sapropterin dihydrochloride tablets, is a synthetic preparation of the dihydrochloride salt of naturally occurring tetrahydrobiopterin (BH4). Sapropterin dihydrochloride is white to off-white crystalline powder.

The chemical name of sapropterin dihydrochloride is (6R)-2-amino-6-\{(1R,2S)-1,2-dihydroxypropyl\}-5,6,7,8-tetrahydro-4(1H)-pteridinone dihydrochloride and the molecular formula is C$_9$H$_{15}$N$_5$O$_7$·2HCl with a molecular weight of 314.17.

Sapropterin dihydrochloride has the following structural formula:

![Structural formula of sapropterin dihydrochloride](image)

Sapropterin dihydrochloride is supplied as tablets containing 100 mg of sapropterin dihydrochloride (equivalent to 76.8 mg of sapropterin base).

Tablets are off-white to light yellow, mottled, uncoated, round shaped tablets debossed with ‘P’ on one side and ‘720’ on other side. Each tablet contains the following inactive ingredients: ascorbic acid, colloidal silicon dioxide, copovidone, crospovidone, dibasic calcium phosphate anhydrous, mannitol, riboflavin and sodium stearyl fumarate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sapropterin dihydrochloride is a synthetic form of BH4, the cofactor for the enzyme phenylalanine hydroxylase (PAH). PAH hydroxylates Phe through an oxidative reaction to form tyrosine. In patients with PKU, PAH activity is absent or deficient. Treatment with BH4 can activate residual PAH enzyme activity, improve the normal oxidative metabolism of Phe, and decrease Phe levels in some patients.

12.2 Pharmacodynamics

In PKU patients who are responsive to BH4 treatment, blood Phe levels decrease within 24 hours after a single administration of sapropterin dihydrochloride, although maximal effect on Phe level may take up to a month, depending on the patient. A single daily dose of sapropterin dihydrochloride is adequate
to maintain stable blood Phe levels over a 24-hour period. Twelve patients with blood Phe levels ranging from 516 to 986 µmol/L (mean 747±153 µmol/L) were assessed with 24-hour blood Phe level monitoring following a daily morning dose of 10 mg/kg per day. The blood Phe level remained stable during a 24-hour observation period. No substantial increases in blood Phe levels were observed following food intake throughout the 24-hour period.

Sapropterin dihydrochloride dose-response relationship was studied in an open-label, forced titration study at doses of 5 mg/kg per day, then 20 mg/kg per day, and then 10 mg/kg per day (Study 3) [see Clinical Studies (14.1)]. Individual blood Phe levels were highly variable among patients. The mean blood Phe level observed at the end of each 2-week dosing period decreased as the dose of sapropterin dihydrochloride increased, demonstrating an inverse relationship between the dose of sapropterin dihydrochloride and mean blood Phe levels.

**Effects of Sapropterin dihydrochloride on the QTc interval**

A thorough QTc study was performed in 56 healthy adults. This randomized, placebo and active controlled crossover study was conducted to determine if a single supra-therapeutic (100 mg/kg) dose of sapropterin dihydrochloride or a single therapeutic dose (20 mg/kg) of sapropterin dihydrochloride had an effect on cardiac repolarization. In this study, sapropterin dihydrochloride was administered after dissolving tablets in water under fed condition. This study demonstrated a dose-dependent shortening of the QT interval. The maximum placebo-subtracted mean change from baseline of the QTc interval was -3.69 and -8.32 ms (lower bound of 90% CI: -5.3 and -10.6 ms) at 20 and 100 mg/kg, respectively.

### 12.3 Pharmacokinetics

Studies in healthy subjects have shown comparable absorption of sapropterin when tablets are dissolved in water or orange juice and taken under fasted conditions. Administration of dissolved tablets after a high-fat/high-calorie meal resulted in mean increases in Cₘₐₓ of 84% and AUC of 87% (dissolved in water). However, there was extensive variability in individual subject values for Cₘₐₓ and AUC across the different modes of administration and meal conditions. In the clinical trials of sapropterin dihydrochloride, drug was administered in the morning as a dissolved tablet without regard to meals. The mean elimination half-life in PKU patients was approximately 6.7 hours (range 3.9 to 17 hours), comparable with values seen in healthy subjects (range 3.0 to 5.3 hours).

A study in healthy adults with 10 mg/kg of sapropterin dihydrochloride demonstrated that the absorption via intact tablet administration was 40% greater than via dissolved tablet administration under fasted conditions based on AUC₀₋₉. The administration of intact tablets under fed conditions resulted in an approximately 43% increase in the extent of absorption compared to fasted conditions based on AUC₀₋₉.

Population pharmacokinetic analysis of sapropterin including patients from 1 month to 49 years of age showed that body weight is the only covariate substantially affecting clearance or distribution volume (see Table 5). Pharmacokinetics in patients >49 years of age have not been studied.

#### Table 5. Apparent Plasma Clearance by Age

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0 to &lt;1 yr* (N=10)</th>
<th>0 to &lt;6 yr* (N=57)</th>
<th>6 to &lt;12 yr† (N=23)</th>
<th>12 to &lt;18 yr† (N=24)</th>
<th>≥18 yr† (N=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL/F (L/hr/kg)</td>
<td>81.5 ± 92.4 (53.6)</td>
<td>50.7 ± 20.1 (48.4)</td>
<td>51.7 ± 21.9 (47.4)</td>
<td>39.2 ± 9.3 (38.3)</td>
<td>37.9 ± 20.2 (31.8)</td>
</tr>
<tr>
<td>Mean ± SD (Median)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Evaluated at 20 mg/kg per day dose  †Evaluated at 5, 10, or 20 mg/kg per day doses

**Metabolism**

Sapropterin is a synthetic form of tetrahydrobiopterin (BH4) and is expected to be metabolized and recycled by the same endogenous enzymes. *In vivo* endogenous BH4 is converted to quinoid dihydrobiopterin and is metabolized to dihydrobiopterin and biopterin. The enzymes dihydrofolate reductase and dihydropyridine reductase are responsible for the metabolism and recycling of BH4.)
Drug Interaction Studies

Clinical Studies

In healthy subjects, administration of a single dose of sapropterin dihydrochloride 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.

In Vitro Studies Where Drug Interaction Potential Was Not Further Evaluated Clinically

The potential for sapropterin to induce or inhibit cytochrome P450 enzymes was evaluated in in vitro studies which showed sapropterin did not inhibit CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5, nor induce CYP 1A2, 2B6, or 3A4/5.

In vitro sapropterin did not inhibit OAT1, OAT3, OCT2, MATE1, and MATE2-K transporters. The potential for sapropterin to inhibit OATP1B1 and OATP1B3 has not been adequately studied. In vitro, sapropterin inhibits breast cancer resistance protein (BCRP) but the potential for a clinically significant increase in systemic exposure of BCRP substrates by sapropterin dihydrochloride appears to be low.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 2-year carcinogenicity study was conducted in F-344 rats, and a 78-week carcinogenicity study was conducted in CD-1 mice. In the 104-week oral carcinogenicity study in rats, sapropterin dihydrochloride doses of 25, 80, and 250 mg/kg per day (0.2, 0.7, and 2 times the maximum recommended human dose of 20 mg/kg per day, respectively, based on body surface area) were used. In the 78-week oral carcinogenicity study in mice, sapropterin dihydrochloride doses of 25, 80, and 250 mg/kg per day (0.1, 0.3, and 2 times the recommended human dose, respectively, based on body surface area) were used. In the 2-year rat carcinogenicity study, there was a statistically significant increase in the incidence of benign adrenal pheochromocytoma in male rats treated with the 250 mg/kg per day (about 2 times the maximum recommended human dose, based on body surface area) dose, as compared to vehicle treated rats. The mouse carcinogenicity study showed no evidence of a carcinogenic effect, but the study was not ideal due to its duration of 78 instead of 104 weeks.

Sapropterin dihydrochloride was genotoxic in the in vitro Ames test at concentrations of 625 µg (TA98) and 5000 µg (TA100) per plate, without metabolic activation. However, no genotoxicity was observed in the in vitro Ames test with metabolic activation. Sapropterin dihydrochloride was genotoxic in the in vitro chromosomal aberration assay in Chinese hamster lung cells at concentrations of 0.25 and 0.5 mM. Sapropterin dihydrochloride was not mutagenic in the in vivo micronucleus assay in mice at doses up to 2000 mg/kg per day (about 8 times the maximum recommended human dose of 20 mg/kg per day, based on body surface area). Sapropterin dihydrochloride, at oral doses up to 400 mg/kg per day (about 3 times the maximum recommended human dose, based on body surface area) was found to have no effect on fertility and reproductive function of male and female rats.

14 CLINICAL STUDIES

The efficacy of sapropterin dihydrochloride was evaluated in five clinical studies in patients with PKU.

Study 1 was a multicenter, open-label, uncontrolled clinical trial of 489 patients with PKU, ages 8 to 48 years (mean 22 years), who had baseline blood Phe levels ≥ 450 µmol/L and who were not on Phe-restricted diets. All patients received treatment with Sapropterin dihydrochloride 10 mg/kg per day for 8 days. For the purposes of this study, response to sapropterin dihydrochloride treatment was defined as a ≥ 30% decrease in blood Phe from baseline. At Day 8, 96 patients (20%) were identified as responders.

Study 2 was a multicenter, double-blind, placebo-controlled study of 88 patients with PKU who responded to sapropterin dihydrochloride in Study 1. After a washout period from Study 1, patients were randomized equally to either sapropterin dihydrochloride 10 mg/kg per day (N=41) or placebo (N=47) for 6 weeks. 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
The results showed that at baseline, the mean (±SD) blood Phe level was 843 (±300) µmol/L in the sapropterin dihydrochloride-treated group and 888 (±323) µmol/L in the placebo group. At Week 6, the sapropterin dihydrochloride treated group had a mean (±SD) blood Phe level of 607 (±377) µmol/L, and the placebo group had a mean blood Phe level of 891 (±348) µmol/L. At Week 6, the sapropterin dihydrochloride- and placebo treated groups had mean changes in blood Phe level of –239 and 6 µmol/L, respectively (mean percent changes of –29% (±32) and 3% (±33), respectively). The difference between the groups was statistically significant (p<0.001) (Table 6).

Table 6: Blood Phe Results in Study 2

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<th>Sapropterin (N=41)</th>
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<tr>
<td><em><em>Baseline Blood Phe Level</em> (µmol/L)</em>*</td>
<td></td>
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<tr>
<td>Mean (±SD)</td>
<td>843 (±300)</td>
<td>888 (±323)</td>
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<tr>
<td>Percentiles (25th, 75th)</td>
<td>620, 990</td>
<td>618, 1141</td>
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<td><strong>Week 6 Blood Phe Level (µmol/L)</strong></td>
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<tr>
<td>Mean (±SD)</td>
<td>607 (±377)</td>
<td>891 (±348)</td>
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<tr>
<td>Percentiles (25th, 75th)</td>
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<td>619, 1143</td>
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<tr>
<td><strong>Mean Change in Blood Phe From Baseline to Week 6 (µmol/L)</strong></td>
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<tr>
<td>Adjusted Mean (±SE)†</td>
<td>-239 (±38)</td>
<td>6 (±36)</td>
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<tr>
<td>Percentiles (25th, 75th)</td>
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<td>-96, 93</td>
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<tr>
<td><strong>Mean Percent Change in Blood Phe From Baseline to Week 6</strong></td>
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<td></td>
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<tr>
<td>Mean (±SD)</td>
<td>-29 (±32)</td>
<td>3 (±33)</td>
</tr>
<tr>
<td>Percentiles (25th, 75th)</td>
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<td>-13, 12</td>
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</tbody>
</table>

*The mean baseline levels shown in this table represent the mean of 3 pretreatment levels (Wk -2, Wk -1, and Wk 0). Treatment with sapropterin dihydrochloride or placebo started at Wk 0.

†p-value < 0.001, adjusted mean and standard error from an ANCOVA model with change in blood Phe level from baseline to Week 6 as the response variable, and both treatment group and baseline blood Phe level as covariates.

Change in blood Phe was noted in the sapropterin dihydrochloride-treated group at Week 1 and was sustained through Week 6 (Figure 2).

Figure 2: Mean Blood Phenylalanine (Phe) Level Over Time*
Study 3 was a multicenter, open-label, extension study in which 80 patients who responded to sapropterin dihydrochloride treatment in Study 1 and completed Study 2 underwent 6 weeks of forced dose-titration with 3 different doses of sapropterin dihydrochloride. Treatments consisted of 3 consecutive 2-week courses of sapropterin dihydrochloride at doses of 5, then 20, and then 10 mg/kg per day. Blood Phe level was monitored after 2 weeks of treatment at each dose level. At baseline, mean (±SD) blood Phe was 844 (±398) µmol/L. At the end of treatment with 5, 10, and 20 mg/kg per day, mean (±SD) blood Phe levels were 744 (±384) µmol/L, 640 (±382) µmol/L, and 581 (±399) µmol/L, respectively (Table 7).

Table 7: Blood Phe Results From Forced Dose-Titration in Study 3

<table>
<thead>
<tr>
<th>Sapropterin Dihydrochloride Dose Level (mg/kg per day)</th>
<th>No. of Patients</th>
<th>Mean (±SD) Blood Phe Level (µmol/L)</th>
<th>Mean Changes (±SD) in Blood Phe Level From Week 0 (µmol/L)</th>
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<tbody>
<tr>
<td>Baseline (No Treatment)</td>
<td>80</td>
<td>844 (±398)</td>
<td>—</td>
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<tr>
<td>5</td>
<td>80</td>
<td>744 (±384)</td>
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<td>10</td>
<td>80</td>
<td>640 (±382)</td>
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<tr>
<td>20</td>
<td>80</td>
<td>581 (±399)</td>
<td>-263 (±318)</td>
</tr>
</tbody>
</table>

Study 4 was a multicenter study of 90 pediatric patients with PKU, ages 4 to 12 years, who were on Phe-restricted diets and who had blood Phe levels ≤480 µmol/L at screening. All patients were treated with open-label sapropterin dihydrochloride 20 mg/kg per day for 8 days. Response to sapropterin dihydrochloride was defined as a ≥30% decrease in blood Phe from baseline at Day 8. At Day 8, 50 patients (56%) had a ≥30% decrease in blood Phe.
Study 5 was an open label, single arm, multicenter trial in 93 pediatric patients with PKU, aged 1 month to 6 years, who had Phe levels greater than or equal to 360 μmol/L at screening. All patients were treated with sapropterin dihydrochloride at 20 mg/kg per day and maintained on a Phe-restricted diet. At Week 4, 57 patients (61%) were identified as responders (defined as ≥ 30% decreased in blood Phe from baseline) (see Figure 1 section 8.4).

16 HOW SUPPLIED/STORAGE AND HANDLING

Sapropterin Dihydrochloride Tablets, 100 mg, are off-white to light yellow, mottled, uncoated, round shaped tablets debossed with ‘P’ on one side and ‘720’ on other side. The tablets are supplied as follows:

NDC 49884-720-11       Bottle of 30 tablets
NDC 49884-720-08       Bottle of 120 tablets

Storage

Store sapropterin dihydrochloride tablets at 20º to 25ºC (68º to 77ºF); excursions allowed between 15º to 30ºC (59º to 86ºF) [see USP Controlled Room Temperature]. Keep container tightly closed. Protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Patients should be advised of the following information before beginning treatment with sapropterin dihydrochloride tablets:

- Advise patients that sapropterin dihydrochloride tablets may cause low blood Phe levels. Advise patients that children younger than 7 years treated with sapropterin dihydrochloride tablets doses of 20 mg/kg per day are at increased risk for low levels of blood Phe compared with children 7 years and older. Blood Phe levels that are too low for prolonged periods of time may be associated with catabolism and protein breakdown [see Warnings and Precautions (5.3)].
- Advise patients that sapropterin dihydrochloride tablets are to be used in conjunction with a Phe-restricted diet [see Dosage and Administration (2.1)].
- Advise patients that not all patients with PKU respond to treatment with sapropterin dihydrochloride tablets and that response to sapropterin dihydrochloride tablets can only be determined by a therapeutic trial [see Warnings and Precautions (5.5)].
- Advise patients that they must be evaluated for changes in blood Phe after being treated with sapropterin dihydrochloride tablets at the recommended dose(s) for age to determine if they are a responder and that blood Phe levels and dietary Phe intake should be measured frequently during the first month [see Warnings and Precautions (5.4, 5.5)].
- Advise patients that they should have frequent blood Phe measurements and nutritional counseling with their physician and other members of the health care team knowledgeable in the management of PKU to ensure maintenance of blood Phe levels in the desirable range [see Warnings and Precautions (5.4)].
- Advise patients not to modify their existing dietary Phe intake during the evaluation period in order to get an accurate assessment of the effect of sapropterin dihydrochloride tablets on blood Phe levels.
- Advise patients not to continue treatment with sapropterin dihydrochloride tablets if they are determined to be a non-responder during the evaluation period [see Dosage and Administration (2.1)].
- Advise patients that reduction of blood Phe levels through dietary control is an important determinant of long-term neurologic outcome in PKU patients. Advise patients that the effect of sapropterin dihydrochloride tablets on long-term neurologic function in patients with PKU has not been assessed.
- Advise patients that sapropterin dihydrochloride tablets may cause hypersensitivity reactions including anaphylaxis and rash [see Warnings and Precautions (5.1)].
Advise patients to notify their physician for symptoms of severe gastritis [see Warnings and Precautions (5.2)].

Advise patients that blood Phe levels that are too high for prolonged periods of time can result in neurologic impairment.

Advise patients that adequate blood Phe control needs to be maintained to avoid blood Phe levels that are too high or too low.

Advise patients that to ensure maintenance of adequate blood Phe control, close monitoring is recommended and that the dose of sapropterin dihydrochloride tablets should be adjusted if necessary.

Advise patients who are taking sapropterin dihydrochloride tablets in combination with levodopa that they may require additional clinical monitoring while taking sapropterin dihydrochloride tablets [see Warnings and Precautions (5.6)].

Advise patients who are taking sapropterin dihydrochloride tablets in combination with drugs that inhibit folate metabolism or drugs that inhibit nitric oxide-mediated vasorelaxation may require additional clinical monitoring while taking sapropterin dihydrochloride tablets [see Drug Interactions (7)].

Advise patients that sapropterin dihydrochloride tablets may cause hyperactivity [see Warnings and Precautions (5.7)].

Advise patients that sapropterin dihydrochloride tablets may interact with other drugs. Advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication [see Drug Interactions (7)].

PATIENT INFORMATION

Sapropterin Dihydrochloride Tablets

(SAP-roe-TER-in dye-HYE-droe-KLOR-ide)

What are sapropterin dihydrochloride tablets?

Sapropterin dihydrochloride tablets are a prescription medicine used to lower blood levels of phenylalanine (Phe), in people with a certain type of Phenylketonuria (PKU). Sapropterin dihydrochloride tablets are used along with a Phe-restricted diet.

What should I tell my doctor before taking Sapropterin Dihydrochloride Tablets?

Before you take sapropterin dihydrochloride tablets, tell your doctor about all your medical conditions, including if you:

- are allergic to sapropterin dihydrochloride or any of the ingredients in sapropterin dihydrochloride tablets. See the list of ingredients in sapropterin dihydrochloride tablets at the end of this leaflet.
- have poor nutrition or have loss of appetite.
- are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if sapropterin dihydrochloride tablets passes into your breast milk. Talk to your doctor about the best way to feed your baby if you take sapropterin dihydrochloride tablets.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, herbal, and dietary supplements. Sapropterin dihydrochloride tablets and other medicines may interact with each other. Especially tell your doctor if you take:

- a medicine that contains levodopa
- an antifolate medicine
- sildenafil (Revatio, Viagra), tadalaflil (Adcirca, Cialis), vardenafil (Staxyn, Levitra)

Tell your doctor if you are not sure if your medicine is one that is listed above.
Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take Sapropterin Dihydrochloride Tablets?

- Take sapropterin dihydrochloride tablets exactly as your doctor tells you. Your doctor should tell you how much sapropterin dihydrochloride tablets to take and when to take it.
- Your doctor may change your dose of sapropterin dihydrochloride tablets depending on how you respond to treatment.
- Take Sapropterin dihydrochloride tablets 1 time each day with a meal. It is best to take sapropterin dihydrochloride tablets at the same time each day.
- Sapropterin dihydrochloride tablets comes as a tablet.
  - You can swallow sapropterin dihydrochloride tablets whole or dissolve the tablets in water or apple juice. You may also crush the tablets and mix in a small amount of soft food, such as apple sauce or pudding before taking.
  - See the detailed “Instructions for Use” that comes with sapropterin dihydrochloride tablets for information about the correct way to dissolve and take a dose of sapropterin dihydrochloride tablets.
- It is not possible to know if sapropterin dihydrochloride tablets will work for you until you start taking sapropterin dihydrochloride tablets. Your doctor will check your blood Phe levels when you start taking sapropterin dihydrochloride tablets to see if the medicine is working.
- During treatment with sapropterin dihydrochloride tablets:
  - Any change you make to your diet may affect your blood Phe level. Follow your doctor’s instructions carefully and do not make any changes to your dietary Phe intake without first talking with your doctor. Even if you take sapropterin dihydrochloride tablets, if your Phe blood levels are not well controlled, you can develop severe neurologic problems.
  - Your doctor should continue to monitor your blood Phe levels often during your treatment with sapropterin dihydrochloride tablets, to make sure that your blood Phe levels are not too high or too low.
  - If you have a fever, or if you are sick, your blood Phe level may go up. Tell your doctor as soon as possible so they can change your dose of sapropterin dihydrochloride tablets to help keep your blood Phe levels in the desired range.
  - If you forget to take your dose of sapropterin dihydrochloride tablets, take it as soon as you remember that day. Do not take 2 doses in a day.
  - If you take too much Sapropterin dihydrochloride tablets, call your doctor for advice.

What are the possible side effects of Sapropterin Dihydrochloride Tablets?

Sapropterin dihydrochloride tablets can cause serious side effects, including:

- Severe allergic reactions. Stop taking sapropterin dihydrochloride tablets and get medical help right away if you develop any of these symptoms of a severe allergic reaction:
  - wheezing or trouble breathing
  - flushing
  - coughing
  - nausea
  - feeling lightheaded or you faint
  - rash
- Inflammation of the lining of the stomach (gastritis). Gastritis can happen with sapropterin dihydrochloride tablets and may be severe. Call your doctor right away if you have any of these signs or symptoms:
  - severe upper stomach-area (abdominal) discomfort or pain, nausea and vomiting
  - blood in your vomit or stool
  - black, tarry stools
- Phe levels that are too low. Some children under the age of 7 who take high doses of sapropterin dihydrochloride tablets each day may experience low Phe levels.
- Too much or constant activity (hyperactivity) can happen with sapropterin dihydrochloride
tablets. Tell your doctor if you have any signs of hyperactivity, including:

- fidgeting or moving around too much
- talking too much

The most common side effects of sapropterin dihydrochloride tablets are:

- headache
- runny nose and nasal congestion
- sore throat
- diarrhea
- vomiting
- cough

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of sapropterin dihydrochloride tablets. For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store Sapropterin Dihydrochloride Tablets?**

- Store sapropterin dihydrochloride tablets at room temperature between 68° to 77°F (20° to 25°C).
- Keep sapropterin dihydrochloride tablets in the original bottle with the cap closed tightly.
- Protect from moisture.

Keep sapropterin dihydrochloride tablets and all medicines out of the reach of children.

**General information about the safe and effective use of sapropterin dihydrochloride tablets.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use sapropterin dihydrochloride tablets for a condition for which it was not prescribed. Do not give sapropterin dihydrochloride tablets to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or doctor for information about sapropterin dihydrochloride tablets that is written for health professionals. For more information, go to www.parpharm.com or call Par Pharmaceutical at 1-800-828-9393.

**What are the ingredients in Sapropterin Dihydrochloride Tablets?**

Active ingredient: sapropterin dihydrochloride.

Inactive ingredients: ascorbic acid, colloidal silicon dioxide, copovidone, crospovidone, dibasic calcium phosphate anhydrous, mannitol, riboflavin and sodium stearyl fumarate.

This Patient Information has been approved by the U.S. Food and Drug Administration.

**INSTRUCTIONS FOR USE**

Sapropterin Dihydrochloride Tablets

(SAP-ro-TER-in dye-HYE-droe-KLOR-ide)

Read this Instructions for Use before you start taking sapropterin dihydrochloride tablets and each time you refill your prescription. There may be new information. This information does not take the place of
talking with your healthcare provider about your treatment. Talk to your doctor if you have any questions about the right dose of sapropterin dihydrochloride tablets to take or how to mix it.

**Important information:**
- Sapropterin dihydrochloride comes as a tablet.
- Take sapropterin dihydrochloride tablets exactly as your doctor tells you. Your doctor should tell you how much sapropterin dihydrochloride to take and when to take it.
- Your doctor may change your dose of sapropterin dihydrochloride tablets depending on how you respond to treatment.
- Take sapropterin dihydrochloride tablets 1 time each day with a meal. It is best to take sapropterin dihydrochloride tablets at the same time each day.

**Instructions for taking sapropterin dihydrochloride tablets:**
Sapropterin dihydrochloride tablets can be swallowed whole or dissolved in water or apple juice. You may also crush the tablets and mix in a small amount of soft food, such as apple sauce or pudding.

To dissolve sapropterin dihydrochloride tablets:
- Mix sapropterin dihydrochloride tablets in 4 ounces to 8 ounces (½ cup to 1 cup) of water or apple juice. It may take a few minutes for the tablets to dissolve. To make the tablets dissolve faster, you can stir or crush them.
- The tablets may not dissolve completely. You may see small pieces floating on top of the water or apple juice. This is normal and safe for you to swallow.
- Drink within 15 minutes.
- After drinking your medicine, if you still see small pieces of the tablet, add more water or apple juice and drink to make sure that you take all of your medicine.

**How should I store sapropterin dihydrochloride tablets?**
- Store sapropterin dihydrochloride tablets at room temperature between 68° to 77°F (20° to 25°C).
- Keep sapropterin dihydrochloride tablets in the original bottle with the cap closed tightly.
- Protect from moisture.

**Keep sapropterin dihydrochloride tablets and all medicines out of the reach of children.**

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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Dist. by:

**Par Pharmaceutical**
Chestnut Ridge, NY 10977 U.S.A.

Mfg. by:

**Par Formulations Private Limited,**
9/215, Pudupakkam, Kelambakkam - 603 103.
Made in India
Mfg. Lic. No.: TN00002121
OS720-01-74-01
Issued: 05/2019

**PACKAGE LABEL PRINCIPAL DISPLAY PANEL**
Sapropterin Dihydrochloride Tablets, 100 mg - 30 Tablets - Container Label
**SAPROPTERIN DIHYDROCHLORIDE**
sapropterin dihydrochloride tablet

### Product Information

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### Active Ingredient/Active Moiety

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**Labeler** - Par Pharmaceutical, Inc. (092733690)

Revised: 5/2019

Par Pharmaceutical, Inc.