

## HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use SAPROTERIN DIHYDROCHLORIDE POWDER FOR ORAL SOLUTION safely and effectively. See full prescribing information for SAPROTERIN DIHYDROCHLORIDE POWDER FOR ORAL SOLUTION.**

### SAPROTERIN DIHYDROCHLORIDE powder for oral solution

**Initial U.S. Approval: 2007**

## RECENT MAJOR CHANGES

Warnings and Precautions	
Upper Gastrointestinal Mucosal Inflammation (5.2)	12/2019

## INDICATIONS AND USAGE

Saproterin dihydrochloride powder for oral solution is a phenylalanine hydroxylase activator indicated to reduce blood phenylalanine (Phe) levels in adult and pediatric patients one month of age and older with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin-(BH4)- responsive Phenylketonuria (PKU). Saproterin dihydrochloride powder for oral solution is to be used in conjunction with a Phe-restricted diet. (1)

## DOSAGE AND ADMINISTRATION

All patients with PKU who are being treated with saproterin dihydrochloride powder for oral solution should also be treated with a Phe-restricted diet, including dietary protein and Phe restriction. (2.1)

### Starting Dosage

- Pediatric patients 1 month to 6 years:* The recommended starting dose of saproterin dihydrochloride powder for oral solution is 10 mg/kg taken once daily. (2.1)
- Patients 7 years and older:* The recommended starting dose of saproterin dihydrochloride powder for oral solution is 10 to 20 mg/kg taken once daily. (2.1)

### Dosage Adjustment

- Doses of saproterin dihydrochloride powder for oral solution may be adjusted in the range of 5 to 20 mg/kg taken once daily. (2.1)
  - Monitor blood Phe regularly, especially in pediatric patients. (2.1, 5.3)
- Preparation and Administration**
- Take with a meal. (2.2)
  - 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

- Powder for Oral Solution: 500 mg saproterin dihydrochloride. (3)

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### 1 INDICATIONS AND USAGE

- Dosage
- Preparation and Administration Instructions

### 3 DOSAGE FORMS AND STRENGTHS

### 4 CONTRAINDICATIONS

### 5 WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions Including Anaphylaxis
- Upper Gastrointestinal Mucosal Inflammation
- Hypophenylalaninemia
- Monitoring Blood Phe Levels During Treatment
- Lack of Biochemical Response to Saproterin Dihydrochloride
- Interaction with Levodopa
- Hyperactivity

### 6 ADVERSE REACTIONS

- Clinical Trials Experience
- Postmarketing Experience

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

Saproterin dihydrochloride powder for oral solution is indicated to reduce blood phenylalanine (Phe) levels in adult and pediatric patients one month of age and older with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin-(BH4)- responsive Phenylketonuria (PKU). Saproterin dihydrochloride powder for oral solution is to be used in conjunction with a Phe-restricted diet.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Dosage

Treatment with saproterin dihydrochloride powder for oral solution should be directed by physicians knowledgeable in the management of PKU.

All patients with PKU who are being treated with saproterin dihydrochloride powder for oral solution should also be treated with a Phe-restricted diet, including dietary protein and Phe restriction.

#### Starting Dosage

*Pediatric Patients 1 month to 6 years:* The recommended starting dose of saproterin dihydrochloride powder for oral solution is 10 mg/kg taken once daily.

*Patients 7 years and older:* The recommended starting dose of saproterin dihydrochloride powder for oral solution is 10 to 20 mg/kg taken once daily.

#### Dosage Adjustment (Evaluation Period)

Existing dietary protein and Phe intake should not be modified during the evaluation period.

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 saproterin dihydrochloride powder for oral solution at 10 mg/kg per day for a period of up to 1 month. Blood Phe levels should be checked after 1 week of saproterin dihydrochloride powder for oral solution 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 do not show a biochemical response and treatment with saproterin dihydrochloride powder for oral solution 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 saproterin dihydrochloride powder for oral solution at 20 mg/kg per day for a period of 1 month. Blood Phe levels should be checked after 1 week of saproterin dihydrochloride powder for oral solution treatment and periodically during the first month. Treatment should be discontinued in patients who do not show a biochemical response (blood Phe does not decrease) after 1 month of treatment at 20 mg/kg per day [see *Warnings and Precautions (5.4)*].

Once responsiveness to saproterin dihydrochloride powder for oral solution has been established, the dosage may be adjusted within the range of 5 to 20 mg/kg per day according to biochemical response to therapy (blood Phe). Periodic blood Phe monitoring is recommended to assess blood Phe control, especially in pediatric patients [see *Warnings and Precautions (5.3)*].

#### 2.2 Preparation and Administration Instructions

Take saproterin dihydrochloride powder for oral solution orally with a meal, preferably at the same time each day [see *Clinical Pharmacology (12.3)*]. A missed dose should be taken as soon as possible, but two doses should not be taken on the same day.

#### Saproterin Dihydrochloride Powder for Oral Solution

*Patients weighing greater than 10 kg*

Saproterin dihydrochloride powder for oral solution should be dissolved in 120 to 240 mL of water or apple juice and taken orally within 30 minutes of dissolution. Saproterin dihydrochloride powder for oral solution may also be stirred in a small amount of soft foods such as apple sauce or pudding. Empty the contents of the packet(s) in water, apple juice, or a small amount of soft foods and mix thoroughly. The powder should dissolve completely.

*Patients weighing 10 kg or less (use 100 mg packets)*

For infants weighing 10 kg or less, saproterin dihydrochloride powder for oral solution can be dissolved in as little as 5 mL of water or apple juice and a portion of this solution corresponding to a 10 mg/kg dose may be administered orally via an oral dosing syringe. Table 1 provides dosing information for infants at the recommended starting dose of 10 mg/kg per day. Refer to Table 2 for dosing information at 20 mg/kg per day if dosage adjustment is needed.

**Table 1: 10 mg/kg per day Dosing Table for Infants Weighing 10 kg or less**

Patient Weight (kg)	Dose (mg)	Starting Dose: 10 mg/kg per day <sup>a</sup>		
		Saproterin Dihydrochloride Powder for Oral Solution 100 mg Packets Dissolved <sup>b</sup>	Dilution Volume (mL) <sup>c</sup>	Administered Dose volume (mL) <sup>d</sup>
1	10	1	10	1
2	20	1	10	2
3	30	1	10	3
4	40	1	10	4
5	50	1	10	5
6	60	1	5	3
7	70	1	5	3.5
8	80	1	5	4
9	90	1	5	4.5
10	100	1	5	5

<sup>a</sup>Starting dose for infants is 10 mg/kg per day. Dosing information for 20 mg/kg per day is provided in Table 2.

<sup>b</sup>Powder for oral solution provided in single use packets containing 100 mg saproterin dihydrochloride per packet<sup>c</sup>Volume of water or apple juice to dissolve Saproterin Dihydrochloride Powder for Oral Solution.

<sup>d</sup>Discard remainder of mixture after volume to be administered is drawn.

**Table 2: 20 mg/kg per day Dosing Table for Infants Weighing 10 kg or less**

Patient Weight (kg)	Dose (mg)	20 mg/kg per day		
		Saproterin Dihydrochloride Powder for Oral Solution 100 mg Packets <sup>a</sup> Dissolved	Dilution Volume (mL) <sup>b</sup>	Administered Dose volume (mL) <sup>c</sup>
1	20	1	5	1
2	40	1	5	2
3	60	1	5	3
4	80	1	5	4
5	100	1	5	5
6	120	2	5	3
7	140	2	5	3.5
8	160	2	5	4
9	180	2	5	4.5
10	200	2	5	5

<sup>a</sup>Powder for oral solution provided in single use packets containing 100 mg saproterin dihydrochloride per packet<sup>b</sup>Volume of water or apple juice to dissolve Saproterin Dihydrochloride Powder for Oral Solution.

<sup>c</sup>Discard remainder of mixture after volume to be administered is drawn.

## CONTRAINDICATIONS

None. (4)

## WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions including anaphylaxis:** Saproterin dihydrochloride is not recommended in patients with a history of anaphylaxis to saproterin dihydrochloride; discontinue treatment in patients who experience anaphylaxis and initiate appropriate medical treatment. Continue dietary Phe restrictions. (5.1)
- Upper Gastrointestinal Mucosal Inflammation:** Monitor patients for signs and symptoms of these conditions including esophagitis and gastritis. (5.2)
- Hypophenylalaninemia:** Pediatric patients younger than 7 years treated with saproterin 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. (5.3)
- Monitoring Blood Phe Levels During Treatment:** Ensure adequate blood Phe control and nutritional balance during treatment with saproterin dihydrochloride. Frequent blood monitoring is recommended, especially in pediatric patients. (5.4, 2.1)
- Lack of Biochemical Response to Saproterin Dihydrochloride Treatment:** Response to saproterin dihydrochloride treatment cannot be pre-determined by laboratory (e.g., molecular) testing and can only be determined by a therapeutic trial of saproterin dihydrochloride. (5.5, 2.1)
- Interaction with Levodopa:** Seizures, over-stimulation or irritability may occur; monitor patients for a change in neurologic status. (5.6, 7)
- Hyperactivity:** 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 1-800-826-9393, or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

## DRUG INTERACTIONS

- Inhibitors of Folate Synthesis** (e.g., methotrexate, valproic acid, phenobarbital, trimethoprim): Can decrease endogenous BH4 levels; monitor blood Phe levels more frequently and adjust saproterin dihydrochloride dosage as needed. (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.

Issued: 03/2020

## 7 DRUG INTERACTIONS

### 8 USE IN SPECIFIC POPULATIONS

- Pregnancy
- Lactation
- Pediatric Use
- Geriatric Use

### 10 OVERDOSAGE

### 11 DESCRIPTION

### 12 CLINICAL PHARMACOLOGY

- Mechanism of Action
- Pharmacodynamics
- Pharmacokinetics

### 13 NONCLINICAL TOXICOLOGY

- Carcinogenesis, Mutagenesis, Impairment of Fertility

### 14 CLINICAL STUDIES

### 16 HOW SUPPLIED/STORAGE AND HANDLING

### 17 PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the Full Prescribing Information are not listed

## 3 DOSAGE FORMS AND STRENGTHS

Saproterin dihydrochloride powder for oral solution is available as a unit dose packet containing 500 mg of saproterin dihydrochloride (equivalent to 384 mg of saproterin base). The powder is off-white to lightly yellow in color.

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hypersensitivity Reactions Including Anaphylaxis

Saproterin dihydrochloride is not recommended in patients with a history of anaphylaxis to saproterin 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 saproterin dihydrochloride in patients who experience anaphylaxis and initiate appropriate medical treatment. Continue dietary protein and Phe restriction in patients who experience anaphylaxis.

### 5.2 Upper Gastrointestinal Mucosal Inflammation

Gastrointestinal (GI) adverse reactions suggestive of upper GI mucosal inflammation have been reported with saproterin dihydrochloride. Serious adverse reactions included esophagitis and gastritis [see *Adverse Reactions (6.2)*]. If left untreated, these could lead to severe sequelae including esophageal stricture, esophageal ulcer, gastric ulcer, and bleeding and such complications have been reported in patients receiving saproterin dihydrochloride. Monitor patients for signs and symptoms of upper GI mucosal inflammation.

### 5.3 Hypophenylalaninemia

In clinical trials of saproterin dihydrochloride, some PKU patients experienced hypophenylalaninemia (low blood Phe) during treatment with saproterin dihydrochloride. In a clinical study of pediatric patients younger than 7 years old treated with saproterin dihydrochloride 20 mg/kg per day, the incidence of hypophenylalaninemia was higher than in clinical trials of older patients [see *Adverse Reactions (6.1)*].

### 5.4 Monitoring Blood Phe Levels During Treatment

Prolonged elevations of blood Phe levels in patients with PKU can result in severe neurologic damage, including severe intellectual disability, developmental delay, microcephaly, delayed speech, seizures, and behavioral abnormalities. Conversely, prolonged levels of blood Phe that are too low have been associated with catabolism and endogenous protein breakdown, which has been associated with adverse developmental outcomes. Active management of dietary Phe intake while taking saproterin 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 Lack of Biochemical Response to Saproterin Dihydrochloride

Some patients with PKU do not show biochemical response (reduction in blood Phe) with treatment with saproterin dihydrochloride. In two clinical trials at a saproterin dihydrochloride dose of 20 mg/kg per day, 56% to 75% of pediatric PKU patients showed a biochemical response to saproterin dihydrochloride, and in one clinical trial at a dose of 10 mg/kg per day, 20% of adult and pediatric PKU patients showed a biochemical response to saproterin dihydrochloride [see *Clinical Studies (14)*].

Biochemical response to saproterin dihydrochloride treatment cannot generally be pre-determined by laboratory testing (e.g., molecular testing), and should be determined through a therapeutic trial (evaluation) of saproterin dihydrochloride response [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 saproterin product, 3 patients with underlying neurological disorders experienced seizures, exacerbation of seizures, over-stimulation, and irritability during co-administration of levodopa and saproterin. Monitor patients who are receiving levodopa for changes in neurological status during treatment with saproterin dihydrochloride [see *Drug Interactions (7)*].

### 5.7 Hyperactivity

In the saproterin dihydrochloride post-marketing safety surveillance program, 2 patients with PKU experienced hyperactivity when treated with saproterin dihydrochloride [see *Adverse Reactions (6.2)*]. 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 saproterin dihydrochloride was evaluated in 7 clinical studies in patients with PKU (aged 1 month to 50 years) [see *Clinical Studies (14)*].

In Studies 1 to 4 (controlled and uncontrolled studies), 579 patients with PKU aged 4 to 49 years received saproterin 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 saproterin 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 saproterin 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 Saproterin Dihydrochloride**

MedDRA Preferred Term	Treatment	
	Saproterin Dihydrochloride (N=74)	Placebo (N=59)
	No. Patients (%)	No. Patients (%)
Headache	11 (15)	8 (14)
Rhinorrhea	8 (11)	0
Pharyngolaryngeal pain	7 (10)	1 (2)
Diarrhea	6 (8)	3 (5)
Vomiting	6 (8)	4 (7)
Cough	5 (7)	3 (5)
Nasal congestion	3 (4)	0

In open-label, uncontrolled clinical trials (Studies 1 and 3) all patients received saproterin 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 saproterin 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 saproterin 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 saproterin 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 saproterin 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 saproterin 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 saproterin 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 subjects 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 (saproterin) in approximately 19 controlled and uncontrolled clinical trials. In these clinical trials, subjects were administered saproterin 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 saproterin administration were seizures, exacerbation of seizures [see *Warnings and Precautions (5.3)*], 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 Postmarketing Experience

The following adverse reactions have been reported during post-approval use of saproterin 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 a causal relationship to drug exposure.

*Hypersensitivity reactions including anaphylaxis and rash:* Most hypersensitivity reactions occurred within several days of initiating treatment [see *Warnings and Precautions (5.1)*].

*Gastrointestinal reactions:* esophagitis, gastritis, oropharyngeal pain, pharyngitis, esophageal pain, abdominal pain, dyspepsia, nausea, and vomiting [see *Warnings and Precautions (5.2)*].

*Hyperactivity:* Two cases have been reported. In one case, the patient received an accidental overdose of saproterin dihydrochloride [see *Warnings and Precautions (5.6)*, *Overdosage (10)*].

## 7 DRUG INTERACTIONS

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

**Table 4: Clinically Relevant Drug Interactions**

Levodopa	
<i>Clinical Impact</i>	Saproterin dihydrochloride may increase the availability of tyrosine, a precursor of levodopa. Neurologic events were reported post-marketing in patients receiving saproterin and levodopa concomitantly for a non-PKU indication [see <i>Warnings and Precautions (5.5)</i> ]
<i>Intervention</i>	Monitor patients for a change in neurologic status.
<b>Inhibitors of Folate Synthesis</b> (e.g., methotrexate, valproic acid, phenobarbital, trimethoprim)	
<i>Clinical Impact</i>	<i>In vitro</i> and <i>in vivo</i> nonclinical data suggest that drugs that inhibit folate synthesis may decrease the bioavailability of endogenous BH4 by inhibiting the enzyme dihydrofolate reductase, which is involved in the recycling (regeneration) of BH4. This reduction in net BH4 levels may increase Phe levels.
<i>Intervention</i>	Consider monitoring blood Phe levels more frequently during concomitant administration. An increased dosage of saproterin dihydrochloride may be necessary to achieve a biochemical response.
<b>Drugs Affecting Nitric Oxide-Mediated Vasorelaxation</b> (e.g., PDE-5 inhibitors such as sildenafil, vardenafil, or tadalafil)	
<i>Clinical Impact</i>	Both saproterin 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.
<i>Intervention</i>	Monitor blood pressure.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

An embryo-fetal development study with saproterin 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 saproterin dihydrochloride during the period of organogenesis, a rare defect, holoprosencephaly, was noted at 10 times the MRHD.

All pregnancies have a background risk of major birth defects, pregnancy loss, or other adverse pregnancy outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The estimated background risk of major birth defects and miscarriage in pregnant women with PKU who maintain blood phenylalanine concentrations greater than 600 micromol/L during pregnancy is greater than the corresponding background risk for pregnant women without PKU.

#### Clinical Considerations

##### Disease-Associated Maternal and/or Embryo-Fetal Risk

Uncontrolled blood phenylalanine concentrations before and during pregnancy are associated with an increased risk of adverse pregnancy outcomes and fetal adverse effects. To reduce the risk of hyperphenylalaninemia-induced fetal adverse effects, blood phenylalanine concentrations should be maintained between 120 and 360 micromol/L during pregnancy and during the 3 months before conception [see *Dosage and Administration 2.1*].

#### Data

##### Human Data

##### Uncontrolled Maternal PKU

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. Control of blood phenylalanine 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 saproterin 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).

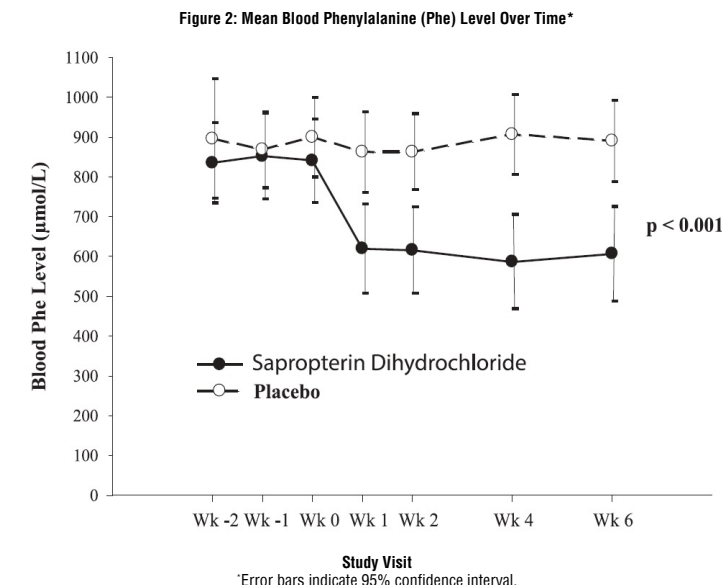
### 8.2 Lactation

#### Risk Summary



<sup>†</sup>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).



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**

Sapropterin Dihydrochloride Dose Level (mg/kg per day)	No. of Patients	Mean (±SD) Blood Phe Level (µmol/L)	Mean Change (±SD) in Blood Phe Level From Week 0 (µmol/L)
Baseline (No Treatment)	80	844 (±398)	–
5	80	744 (±384)	-100 (±295)
10	80	640 (±382)	-204 (±303)
20	80	581 (±399)	-263 (±318)

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 <460 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% decrease in blood Phe from baseline) (see Figure 1 section 8.4).

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### Sapropterin Dihydrochloride Powder for Oral Solution

Supplied as a off-white to lightly yellow powder suspended in unit dose packets as:

500 mg sapropterin dihydrochloride per packet:	
NDC 49884-873-72	Carton of 30 unit dose packets
NDC 49884-873-52	Single unit dose packet

### Storage

Store sapropterin dihydrochloride powder for oral solution at 20° to 25°C (68° to 77°F); excursions allowed between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.

## 17 PATIENT COUNSELING INFORMATION

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

### Hypersensitivity Reactions Including Anaphylaxis

Advise patients and caregivers to discontinue sapropterin dihydrochloride powder for oral solution and contact the patient's healthcare provider immediately if they experience symptoms of anaphylaxis, including (but not limited to) wheezing, dyspnea, coughing, hypotension, flushing, nausea, and rash. Continue nutritional management including dietary protein and Phe restriction [see *Warnings and Precautions* (5.1)].

### Upper Gastrointestinal Mucosal Inflammation

Advise patients and caregivers to contact their healthcare provider if the patient experiences signs and symptoms suggestive of upper GI mucosal inflammation, including nausea, vomiting, dysphagia, dyspepsia, loss of appetite, oropharyngeal, esophageal, or upper abdominal pain [see *Warnings and Precautions* (5.3)].

### Hypophenylalaninemia [see *Warnings and Precautions* (5.3)]

Advise patients and caregivers that sapropterin dihydrochloride powder for oral solution may cause hypophenylalaninemia (low blood Phe levels), especially in pediatric patients younger than 7 years of age.

### Monitoring of Blood Phe Levels [see *Warnings and Precautions* (5.4)]

Advise patients and caregivers that frequent blood Phe monitoring is important to ensure blood Phe levels are in the desirable range and that they should maintain dietary protein and Phe restriction while on sapropterin dihydrochloride powder for oral solution.

Prolonged hyperphenylalaninemia (high blood Phe levels) in patients with PKU can result in severe neurologic damage, including intellectual disability, developmental delay, microcephaly, delayed speech, seizures, and behavioral abnormalities.

### Lack of Biochemical Response to Sapropterin Dihydrochloride Powder for Oral Solution

Some patients do not show a biochemical response (blood Phe reduction) when treated with sapropterin dihydrochloride powder for oral solution. Advise patients and caregivers to discontinue treatment with sapropterin dihydrochloride powder for oral solution if the patient does not show an adequate biochemical response in blood Phe after one month of treatment with sapropterin dihydrochloride powder for oral solution 20 mg/kg per day [see *Dosage and Administration* (2.1), *Warnings and Precautions* (5.4)].

### Interaction with Levodopa

Advise patients and caregivers that patients with underlying neurological disorders taking sapropterin dihydrochloride powder for oral solution in combination with levodopa may experience seizures, exacerbation of seizures, overstimulation or irritability. Inform patients and caregivers to contact their healthcare provider if the patient has a change in neurologic status during treatment with sapropterin dihydrochloride powder for oral solution [see *Warnings and Precautions* (5.5)].

### Hyperactivity

Advise patients and caregivers that sapropterin dihydrochloride powder for oral solution may cause hyperactivity and to contact their healthcare provider if the patient experiences hyperactivity, restlessness, fidgeting, or excessive talking [see *Warnings and Precautions* (5.6)].

### Dosing and Monitoring [see *Dosage and Administration* (2.1)]

Advise patients and caregivers of the following:

- Sapropterin dihydrochloride powder for oral solution should be used in conjunction with a PKU-specific diet, including dietary protein and Phe restriction.
- Dietary protein and Phe intake should not be modified during the sapropterin dihydrochloride powder for oral solution evaluation period when assessing biochemical response.
- The patient must be evaluated for changes in blood Phe after being treated with sapropterin dihydrochloride powder for oral solution at the recommended dose(s) for age to determine if they have a biochemical response and that blood Phe levels and dietary Phe intake should be assessed frequently during the first month of sapropterin dihydrochloride powder for oral solution treatment.
- Monitoring of blood Phe levels is important during sapropterin dihydrochloride powder for oral solution treatment.

### Preparation and Administration [see *Dosage and Administration* (2.2)]

Advise patients and caregivers:

- Sapropterin dihydrochloride powder for oral solution should be dissolved in water or apple juice or stirred in a small amount of soft food such as apple sauce or pudding.
- Take sapropterin dihydrochloride powder for oral solution with a meal, preferably at the same time each day.

<b>PATIENT INFORMATION</b> <b>Sapropterin Dihydrochloride Powder for Oral Solution</b> <b>(SAP-roe-TER-in dye-HYE-droe-KLOR-ide)</b>
<b>What is sapropterin dihydrochloride powder for oral solution?</b> Sapropterin dihydrochloride powder for oral solution is a prescription medicine used to lower blood levels of phenylalanine (Phe), in adults and children one month of age and older with a certain type of Phenylketonuria (PKU). Sapropterin dihydrochloride powder for oral solution is used along with a Phe-restricted diet.
<b>What should I tell my doctor before taking sapropterin dihydrochloride powder for oral solution?</b> <b>Before you take sapropterin dihydrochloride powder for oral solution, tell your doctor about all your medical conditions, including if you:</b> <ul style="list-style-type: none"><li>are allergic to sapropterin dihydrochloride or any of the ingredients in sapropterin dihydrochloride powder for oral solution. See the list of ingredients in sapropterin dihydrochloride powder for oral solution at the end of this leaflet.</li><li>have poor nutrition or have loss of appetite.</li><li>are pregnant or plan to become pregnant.</li><li>are breastfeeding or plan to breastfeed. It is not known if sapropterin dihydrochloride passes into your breast milk. Talk to your doctor about the best way to feed your baby if you take sapropterin dihydrochloride powder for oral solution.</li></ul> <b>Tell your doctor about all the medicines you take</b> , including prescription and over-the-counter medicines, vitamins, herbal, and dietary supplements. Sapropterin dihydrochloride powder for oral solution and other medicines may interact with each other. Especially tell your doctor if you take: <ul style="list-style-type: none"><li>a medicine that contains levodopa</li><li>an antifolate medicine</li><li>sildenafil (Revatio, Viagra), tadalafil (Adcirca, Cialis), vardenafil (Staxyn, Levitra)</li></ul> 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.
<b>How should I take sapropterin dihydrochloride powder for oral solution?</b> <ul style="list-style-type: none"><li>Take sapropterin dihydrochloride powder for oral solution exactly as your doctor tells you. Your doctor should tell you how much sapropterin dihydrochloride powder for oral solution to take and when to take it.</li><li>Your doctor may change your dose of sapropterin dihydrochloride powder for oral solution depending on how you respond to treatment.</li><li>Take sapropterin dihydrochloride powder for oral solution 1 time each day with a meal. It is best to take sapropterin dihydrochloride powder for oral solution at the same time each day.</li><li>Sapropterin dihydrochloride comes as powder for oral solution.<ul style="list-style-type: none"><li>Be sure that you know what dose of sapropterin dihydrochloride powder your doctor prescribed and whether you should use sapropterin dihydrochloride 100 mg packets, sapropterin dihydrochloride 500 mg packets, or both types of packets to prepare your dose.</li><li>Open Sapropterin dihydrochloride powder packets only when you are ready to use them.</li><li><b>Sapropterin dihydrochloride powder for oral solution should be dissolved in water or apple juice.</b> You may also mix the powder for oral solution in a small amount of soft food, such as apple sauce or pudding before taking.</li><li>See the detailed "Instructions for Use" that comes with sapropterin dihydrochloride powder for oral solution for information about the correct way to dissolve and take a dose of sapropterin dihydrochloride powder for oral solution.</li></ul></li><li>It is not possible to know if sapropterin dihydrochloride powder for oral solution will work for you until you start taking sapropterin dihydrochloride powder for oral solution. Your doctor will check your blood Phe levels when you start taking sapropterin dihydrochloride powder for oral solution to see if the medicine is working.</li><li>During treatment with sapropterin dihydrochloride powder for oral solution:<ul style="list-style-type: none"><li>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 powder for oral solution, if your Phe blood levels are not well controlled, you can develop severe neurologic problems.</li><li>Your doctor should continue to monitor your blood Phe levels often during your treatment with sapropterin dihydrochloride powder for oral solution, to <b>make sure that your blood Phe levels are not too high or too low.</b></li><li>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 powder for oral solution to help keep your blood Phe levels in the desired range.</li></ul></li><li>If you forget to take your dose of sapropterin dihydrochloride powder for oral solution, take it as soon as you remember that day. Do not take 2 doses in a day.</li><li>If you take too much sapropterin dihydrochloride powder for oral solution, call your doctor for advice.</li></ul>
<b>What are the possible side effects of sapropterin dihydrochloride powder for oral solution?</b> <b>Sapropterin dihydrochloride powder for oral solution can cause serious side effects, including:</b> <ul style="list-style-type: none"><li><b>Severe allergic reactions.</b> Stop taking sapropterin dihydrochloride powder for oral solution and get medical help right away if you develop any of these symptoms of a severe allergic reaction:<ul style="list-style-type: none"><li>wheezing or trouble breathing</li><li>coughing</li><li>feeling lightheaded or you faint</li><li>flushing</li><li>nausea</li><li>rash</li></ul></li><li><b>Inflammation of the lining of the stomach (gastritis) or esophagus (esophagitis).</b> Gastritis or esophagitis can happen with sapropterin dihydrochloride powder for oral solution and may be severe. <b>Call your doctor right away if you have any of these signs or symptoms:</b><ul style="list-style-type: none"><li>severe upper stomach-area (abdominal) discomfort or pain, nausea and vomiting</li><li>blood in your vomit or stool</li><li>black, tarry stools</li><li>difficulty swallowing</li><li>loss of appetite</li><li>pain in the throat</li></ul></li><li><b>Phe levels that are too low.</b> Some children under the age of 7 years who take high doses of sapropterin dihydrochloride powder for oral solution each day may experience low Phe levels.</li><li><b>Too much or constant activity (hyperactivity) can happen with sapropterin dihydrochloride powder for oral solution.</b> Tell your doctor if you have any signs of hyperactivity, including:<ul style="list-style-type: none"><li>fidgeting or moving around too much</li><li>talking too much</li></ul></li></ul>
The most common side effects of sapropterin dihydrochloride powder for oral solution are: <ul style="list-style-type: none"><li>headache</li><li>runny nose and nasal congestion</li><li>sore throat</li><li>diarrhea</li><li>vomiting</li><li>cough</li></ul>
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 powder for oral solution. 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.
<b>How should I store sapropterin dihydrochloride powder for oral solution?</b> <ul style="list-style-type: none"><li>Store sapropterin dihydrochloride powder for oral solution at room temperature between 68° to 77°F (20° to 25°C).</li><li>Protect from moisture.</li></ul> <b>Keep sapropterin dihydrochloride powder for oral solution and all medicines out of the reach of children.</b> <b>General information about the safe and effective use of sapropterin dihydrochloride powder for oral solution.</b> Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use sapropterin dihydrochloride powder for oral solution for a condition for which it was not prescribed. Do not give sapropterin dihydrochloride powder for oral solution 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 powder for oral solution that is written for health professionals. For more information, go to <a href="http://www.parpfarm.com">www.parpfarm.com</a> or call Par Pharmaceutical at 1-800-828-9393.
<b>What are the ingredients in sapropterin dihydrochloride powder for oral solution?</b> <b>Active ingredient:</b> sapropterin dihydrochloride. <b>Inactive ingredients:</b> ascorbic acid, mannitol, potassium citrate and sucralose.
This Patient Information has been approved by the U.S. Food and Drug Administration

## Instructions for Use

### Sapropterin Dihydrochloride Powder for Oral Solution

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

Read these Instructions for Use before you start taking sapropterin dihydrochloride powder for oral solution 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 powder for oral solution to take or how to mix it.

### Important information:

- Sapropterin dihydrochloride comes in a packet containing powder.
- Take sapropterin dihydrochloride powder for oral solution exactly as your doctor tells you. Your doctor should tell you how much sapropterin dihydrochloride powder for oral solution to take and when to take it.
- Your doctor may change your dose of sapropterin dihydrochloride powder for oral solution depending on how you respond to treatment, or based on your baby's weight.
- If your baby weighs 22 pounds or less, follow the section called "**Instructions for giving sapropterin dihydrochloride powder for oral solution (sapropterin dihydrochloride 100 mg packets) to babies who weigh 22 pounds or less**".
- Take sapropterin dihydrochloride powder for oral solution 1 time each day with a meal. It is best to take sapropterin dihydrochloride powder for oral solution at the same time each day.

### Instructions for taking sapropterin dihydrochloride powder for oral solution:

For babies who weigh 22 pounds or less, see the section below called "**Instructions for giving sapropterin dihydrochloride powder for oral solution (sapropterin dihydrochloride 100 mg packets) to babies who weigh 22 pounds or less**."

Sapropterin dihydrochloride powder for oral solution should be dissolved in water or apple juice. The powder for oral solution may also be mixed in a small amount of soft foods, such as apple sauce or pudding.

### To dissolve sapropterin dihydrochloride powder for oral solution:

- Be sure that you know what dose of sapropterin dihydrochloride powder for oral solution your doctor has prescribed and whether you should use sapropterin dihydrochloride 100 mg packets, sapropterin dihydrochloride 500 mg packets, or both types of packets to prepare your dose.
- Open the packet(s) of sapropterin dihydrochloride powder for oral solution by folding and tearing, or cutting at the dotted line in the upper right corner of the packet. Open the packet(s) only when you are ready to use them.
- Empty the contents of the packet(s) into 4 ounces to 8 ounces (1/2 cup to 1 cup) of water or apple juice.
- Drink within 30 minutes.

### Instructions for giving sapropterin dihydrochloride powder for oral solution (sapropterin dihydrochloride 100 mg packets) to babies who weigh 22 pounds or less:

- The dose of sapropterin dihydrochloride powder for oral solution is based on body weight. This will change as your baby grows. Your doctor will tell you:
  - the number of sapropterin dihydrochloride 100 mg packets needed for one dose
  - the amount of water or apple juice needed to mix one dose of sapropterin dihydrochloride powder for oral solution
  - the amount of the mixture (powder and water or apple juice) you will need to give your baby his or her prescribed dose of medicine.
- Give your baby the prescribed amount of mixture (powder and water or apple juice) within 30 minutes after mixing. If you are not able to give your baby's dose within 30 minutes after mixing, pour the unused medicine into the trash. You will need to mix a new dose.

### Supplies needed to mix and give your baby's dose of sapropterin dihydrochloride powder for oral solution:

- the number of sapropterin dihydrochloride 100 mg packets needed for one dose
- a small cup of water or apple juice
- one 30 mL medicine cup for mixing
- small spoon or clean utensil for mixing
- 10 mL oral dosing syringe
- scissors (optional)

Ask your pharmacist for a 30 mL medicine cup for mixing and an oral dosing syringe if you do not have these supplies.

**Step 1:** Find a clean, flat work surface.

**Step 2:** Place a small cup of water or apple juice, the oral dosing syringe, and an empty medicine cup on your clean, flat work surface (see Figure A).

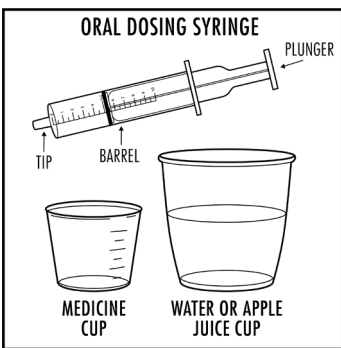


Figure A

**Step 3:** Pour 5 mL or 10 mL of water or apple juice from the small cup into the medicine cup, as instructed by your doctor. Check to make sure that the amount of liquid lines up with the amount that your doctor tells you (see Figure B).

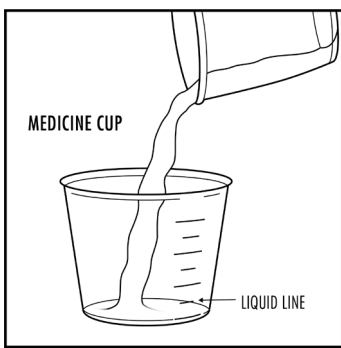


Figure B

**Step 4:** Check the label on the sapropterin dihydrochloride powder for oral solution packet(s). If the packet is marked sapropterin dihydrochloride powder for oral solution 100 mg, empty the entire contents of the sapropterin dihydrochloride powder for oral solution packet into the medicine cup (see Figure C).

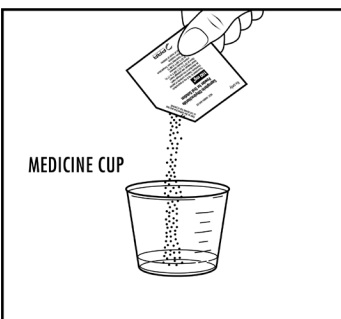


Figure C

**Step 5:** Stir the mixture with the small spoon or other clean utensil until all of the powder completely dissolves (see Figure D).

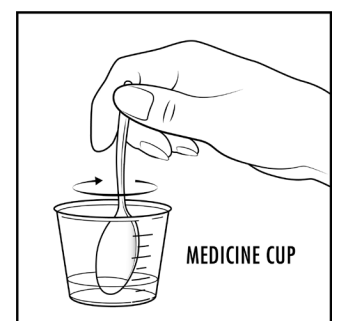


Figure D

**Step 6:** To give a dose of sapropterin dihydrochloride powder for oral solution to your baby, place the tip of the oral dosing syringe into the liquid inside the medicine cup. Pull back on the plunger and draw up the amount of the mixture prescribed by your doctor (see Figure E).

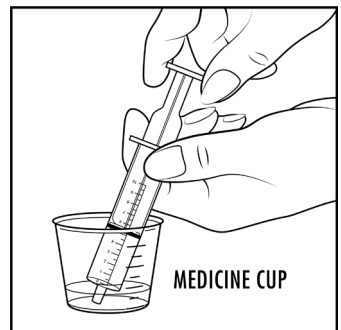


Figure E

**Step 7:** Take the oral dosing syringe out of the medicine cup. Carefully turn the oral dosing syringe so that the tip is pointing up. Check to make sure that the amount of medicine in the oral dosing syringe lines up with the amount of mixture prescribed by your doctor (see Figure F).

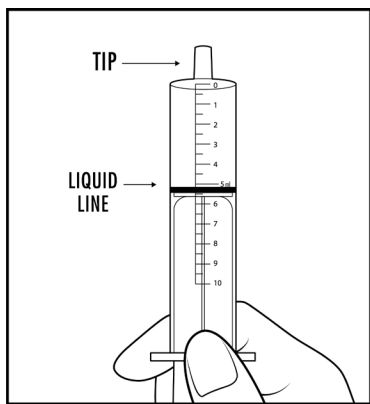


Figure F

**Step 8:** Place the tip of the oral dosing syringe into your baby's mouth. Point the tip of the oral dosing syringe toward either cheek (see Figure G). Push on the plunger slowly, a small amount at a time, until all of the mixture in the oral dosing syringe is given.

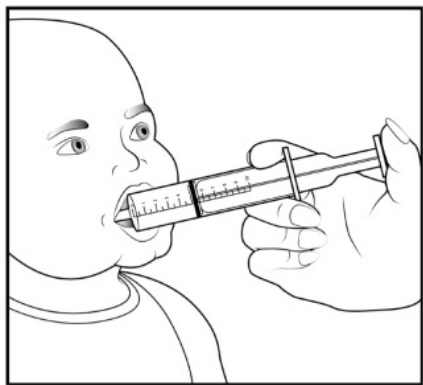


Figure G

**Step 9:** Throw away any remaining mixture. Remove the plunger from the barrel of the oral dosing syringe. Wash the oral dosing syringe and medicine cup with warm water and air dry. When the oral dosing syringe is dry, put the plunger back into the barrel. Store the oral dosing syringe and medicine cup for the next use.

### How should I store sapropterin dihydrochloride powder for oral solution?

- Store sapropterin dihydrochloride powder for oral solution at room temperature between 68° to 77°F (20° to 25°C).
- Protect from moisture.

### Keep sapropterin dihydrochloride powder for oral solution and all medicines out of the reach of children.

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

All brand names listed are the registered trademarks of their respective owners and are not trademarks of Par Pharmaceutical.

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  
OS873-01-74-01

Issued: 03/2020