# Tetrahydrobiopterin Therapy for Phenylketonuria in Infants and Young Children

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**Objective** To describe patient selection, treatment administration, response evaluation, and side effect management associated with sapropterin therapy in infants and children aged <4 years.

**Study design** Six case reports are presented from 4 US metabolic clinics treating phenylketonuria with sapropterin in patients aged 7 months to 4 years. Outcomes included blood phenylalanine (Phe) levels before and during treatment. For 3 of 6 cases, diet records were used to monitor changes in dietary Phe.

**Results** Severity of phenylketonuria ranged from mild to severe (classic). Treatment with sapropterin was safe and generally well tolerated. Blood Phe levels were reduced, or maximum dietary Phe tolerance was increased in patients with blood Phe that was well controlled by diet.

**Conclusions** Given the increasing evidence that maintaining blood Phe levels below 360 μmol/L is important for the normal development of neurocognitive and behavioral function, sapropterin can be combined with a Phe-restricted diet to control blood Phe levels in young patients responsive to sapropterin therapy. *(J Pediatr 2011;158:410-5)*.

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Phenylketonuria (PKU) is an inherited metabolic disorder involving a group of genetic mutations that reduce the ability of the enzyme phenylalanine hydroxylase (PAH) to convert phenylalanine (Phe) to tyrosine, leading to an accumulation of Phe in the blood and brain. Dietary therapy for this disorder has virtually eliminated the incidence of severe mental deficits and other physical ailments (eg, seizures, skin problems, microcephaly) caused by high Phe levels during infancy. However, the Phe-restricted diet has limitations related to cost, palatability, nutritional adequacy, and convenience, which often lead to reduced adherence to the prescribed diet during adolescence. In the past, it was common practice to recommend eliminating the Phe-restricted diet in school-aged children, when brain development was presumed to be complete. Accumulating evidence on behavior and cognitive development suggests that patients who remain on the diet do better than patients who discontinue the diet,[1-5] and it is now standard practice for clinics to recommend a Phe-restricted "diet for life." [6]

In December 2007, the US Food and Drug Administration approved sapropterin dihydrochloride (sapropterin), a synthetic version of the naturally occurring PAH cofactor tetrahydrobiopterin ($BH_4$), for the treatment of PKU. In $BH_4$-responsive patients, sapropterin can be combined with a Phe-restricted diet to further reduce elevated blood Phe levels. Although there are no age restrictions associated with the use of sapropterin in the United States,[7] clinical trials that contributed to the Food and Drug Administration approval included only subjects aged 4 years and older.[8-10] Given the lack of data for this age group, some clinicians have been hesitant to prescribe treatment for patients aged <4 years. Furthermore, sapropterin has been approved for use in the European Union with an age restriction excluding this age group.[11] In the 18 months since sapropterin was approved for use in the United States, a number of clinics have begun treating infants and young children aged <4 years. The objectives of this report are to share the experiences of some of these clinics with regard to patient selection, treatment administration, response evaluation, and side effect management, and to discuss treatment issues associated with this patient population.

## Methods

The methods described herein are applicable to the patient cases presented in the Results section. Case-specific modifications of or additions to these methods are

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|---|---|
| $BH_4$ | Tetrahydrobiopterin |
| OFC | Occipital-frontal circumference |
| PAH | Phenylalanine hydroxylase |
| Phe | Phenylalanine |
| PKU | Phenylketonuria |

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noted in the individual case presentations. Because no clinic has extensive experience with sapropterin treatment in the 0- to 4-year age group, it did not seem appropriate to provide summary statistics based on the small sample sizes for each clinic. Instead, contributing clinics were asked to provide one or two cases that demonstrated an interesting aspect of treatment.

Patients selected for treatment were diagnosed through newborn screening and screened for primary $BH_4$ deficiency. Five out of the 6 patients were started on a Phe-restricted diet by 15 days of life. The blood Phe level for the sixth patient was not sufficiently elevated to warrant treatment after identification by newborn screening, so that patient was never started on the diet. Treatment with sapropterin was initiated between age 7 months and 4 years in patients with baseline blood Phe levels ranging from 72 to 810 $\mu$mol/L.

In general, testing for responsiveness to sapropterin involved determining blood Phe levels just before initiating treatment. Dosing was weight-based, starting at either 10 or 20 mg/kg/day, and tablets were administered by crushing and/or dissolving in water, apple juice, or formula. Parents were advised not to change their child's diet during the period of testing for responsiveness. For 3 of the 6 patients, diet records were available to determine the amount of Phe consumed before and during treatment. Blood Phe levels were tested again at regular intervals (which differed from case to case). Responsiveness to sapropterin was defined as either a clinically significant decline in blood Phe level or a demonstrated increase in dietary Phe tolerance while blood Phe level was maintained within the desired range.

## Results

### Case 1

This girl was diagnosed with classic PKU based on a blood Phe level of 2460 $\mu$mol/L and was started on a diet of Phe-free medical formula at approximately 1 month of age. For the first 3 years of life, the patient and her family were compliant with the Phe-restricted diet, providing daily diet records and blood Phe samples on a regular basis. Blood Phe level remained in excellent control, varying from 30 to 384 $\mu$mol/L (excluding periods of illness), with an average of 192 $\pm$ 90 $\mu$mol/L. A total of 78 measurements were recorded. During this period, the patient developed normally, following the appropriate percentiles for growth in weight, height, and occipital-frontal circumference (OFC).

At age 3 years, 1 month, the patient was tested for responsiveness to sapropterin. When testing was initiated, the patient's diet consisted of 90 g of Phe-free formula and 330 mg of Phe from 6.6 g of natural protein. Her weight was 17 kg. She was started on a sapropterin dose of 300 mg, or 17.6 mg/kg/day. This dose was increased to 400 mg, or 21.4 mg/kg/day, when she reached 18.7 kg in July 2008. The patient's average blood Phe for the 6 levels recorded before the start of treatment was 227 $\pm$ 107 $\mu$mol/L, which was similar to the average for the previous 3 years (192 $\mu$mol/L). As shown in Figure 1, her blood Phe level just before starting treatment (72 $\mu$mol/L) was well below this level. For the first 5 weeks of testing, her blood Phe level averaged 104 $\pm$ 46 $\mu$mol/L, representing a decrease of 54% compared with the mean value before the start of therapy. At this point, dietary Phe tolerance was tested by increasing Phe intake. As Phe intake increased from 330 to 1100 mg/day, blood Phe level increased from 60 to a maximum of 550 $\mu$mol/L. Dietary Phe intake was then decreased and maintained at approximately 900 mg/day. During this period, the average blood Phe level was 192 $\pm$ 65 $\mu$mol/L, representing a 15% decrease relative to pretreatment levels. For this patient, blood Phe level did not decrease substantially relative to baseline, but the patient's dietary Phe intake almost tripled, allowing for a significant increase of natural protein in the diet.

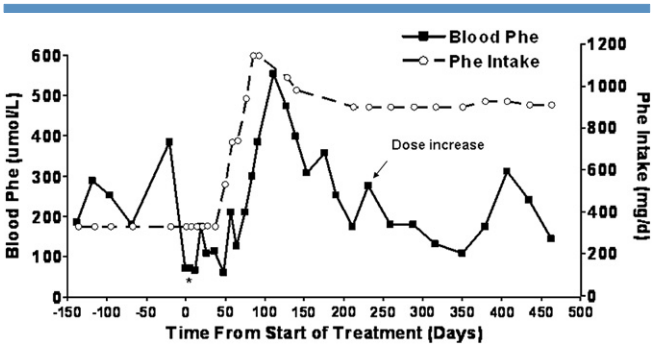


**Figure 1.** Blood Phe levels (left axis) and Phe intake (right axis) for Case 1. Day 0 represents the start of sapropterin treatment. The *arrow* indicates time at which the sapropterin dose was increased.

After maximum Phe tolerance was determined, the patient's Phe intake from foods was slowly increased and Phe from nonfat dry milk was decreased until all 900 mg of Phe was coming from natural protein sources. The patient has slowly added higher-Phe grain products and some yogurt to her diet while decreasing the amount of low-protein foods. There were no reports of adverse events or problems with dosing or administration during treatment, and she has continued to grow and develop normally.

### Case 2

This girl was diagnosed with classic PKU at 7 days after birth, with a blood Phe level of 1902 $\mu$mol/L, at which time she was placed on a Phe-restricted diet of breast milk and Phe-free formula. In the 10 months before starting sapropterin treatment, the patient and family were relatively compliant with the PKU diet and provided blood Phe samples on a regular basis (41 samples). The patient's average blood Phe level was 217 $\pm$ 111 $\mu$mol/L (range, 36-426 $\mu$mol/L). Her dietary Phe intake during this 10-month period ranged from 182 to 289 mg/day (22-63 mg/kg/day). Her development during this period was normal, with consistent growth percentiles for weight, height, and OFC.

At age 10 months, the patient was tested for responsiveness to sapropterin. At the time of testing, she was receiving 235 mg/day of Phe (22 mg/kg/day) through 6.2 g (0.6 g/kg/day) of natural protein and 15.6 g (1.5 g/kg/day) of protein from Phe-free formula. Sapropterin was started at a dose of 200 mg or 18.7 mg/kg/day (initial body weight, 10.7 kg) and was increased to 250 mg to maintain this dose with weight gain. The patient's average blood Phe level for the 5 weeks before the start of treatment (279 ± 159 μmol/L) was similar to her average blood Phe for the previous 10 months (217 μmol/L). As shown in Figure 2, her blood Phe level decreased by 25% relative to baseline in the first 2 weeks of treatment. Over the next 2 weeks, maximum Phe tolerance was determined by adding a cow's milk infant formula to the Phe-free medical formula. Dietary Phe intake was then stabilized at approximately 400 mg/day, and her blood Phe level dropped and became relatively stable at 100-300 μmol/L. During this period, her average blood Phe level was 230 ± 116 μmol/L. As with Case 1, this patient did not experience a substantial decline in blood Phe level during treatment; however, she had a significant increase in dietary Phe intake, from 235 mg/day to 400 mg/day (22 mg/kg/day to approximately 26 mg/kg/day). No adverse events or problems with administration were reported, and she continues to demonstrate normal growth and development during treatment.

## Case 3

This boy was diagnosed at birth with mild to moderate PKU (blood Phe, 558 μmol/L) and was prescribed a Phe-restricted diet. During the first 3 years of life, his blood Phe level was not tracked very closely, and compliance with diet, diet recordkeeping, and blood Phe sampling was poor. The family reported increasing difficulty getting the patient to take Phe-free formula, and his blood Phe level gradually increased to 780 μmol/L. Despite this, the patient continued to grow and develop normally.

At age 3 years, the patient was tested for responsiveness to sapropterin. At the time of testing, his dietary prescription included a Phe-free formula twice daily, but he refused to drink the formula. Dietary Phe intake at this time and during treatment was not reported. Sapropterin was administered at a dose of 200 mg (10 mg/kg/day based on a body weight of 20 kg). The patient's average blood Phe level for the month before starting treatment was 717 ± 87 μmol/L (range, 612-810 μmol/L). For 2 months after the start of treatment, blood Phe level followed a downward trend, averaging 489 ± 110 μmol/L, a decrease of 32% compared with baseline (Figure 3, A). The blood Phe level has continued to decrease, reaching a 60% decrease from baseline. A recent preschool assessment noted advanced developmental progress for the patient's age. Growth and development continue to be normal during sapropterin treatment, and there have been no reports of adverse events.

## Case 4

This girl was diagnosed at birth with classic PKU based on a blood Phe level of 1206 μmol/L. Shortly after birth, she was prescribed a Phe-restricted diet. For the first 3 years of life, her parents had difficulty keeping her compliant with the diet and tracking her Phe intake. During this period, her blood Phe level was often in the range of 900-1080 μmol/L.

At 3 years of age, the patient was tested for responsiveness to sapropterin. Just before starting treatment, she was on a Phe-free formula, but her natural protein intake was not tightly controlled. Her starting dose of sapropterin was 200

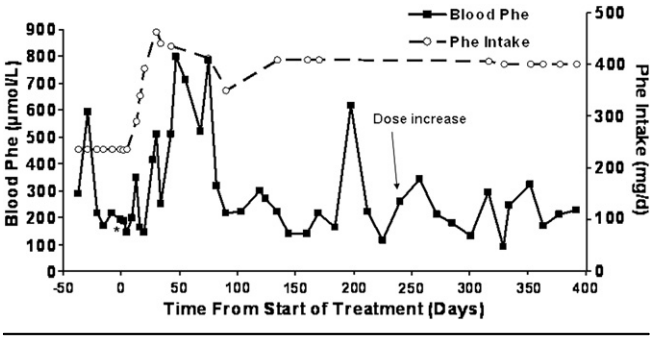


**Figure 2.** Blood Phe levels (left axis) and Phe intake (right axis) for Case 2. Day 0 represents the start of sapropterin treatment. The *arrow* indicates time at which the sapropterin dose was increased.

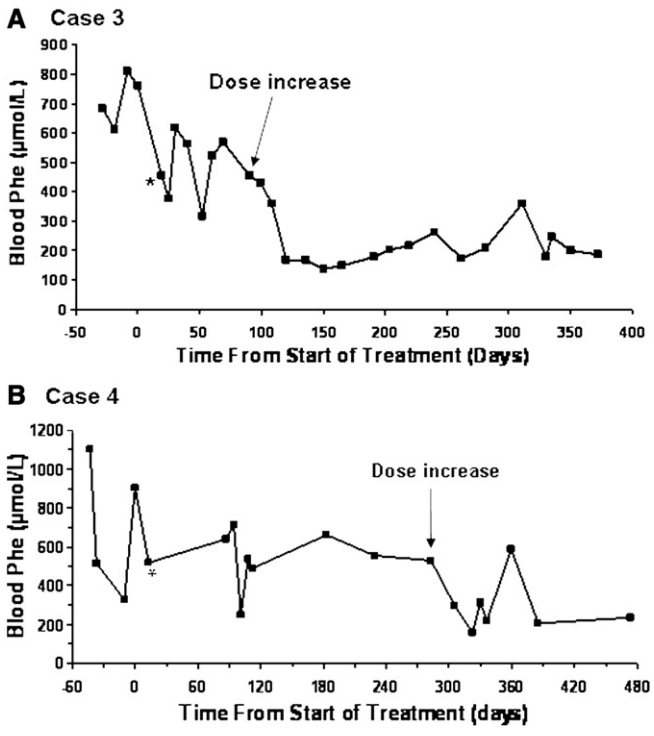


**Figure 3.** Blood Phe levels for **A,** Case 3 and **B,** Case 4. Day 0 represents the start of sapropterin treatment. The *arrows* indicate times at which the sapropterin dose was increased.

mg (13 mg/kg/day based on a body weight of 15 kg). Her average blood Phe level before starting treatment was 711 ± 354 μmol/L. For 9 months after the start of treatment, her blood Phe level averaged 554 ± 64 μmol/L, a decrease of 22% from the baseline average (Figure 3, B).

In an effort to further reduce the patient's blood Phe level, the sapropterin dose was increased to 24 mg/kg/day, 9 months after starting treatment (arrow in Figure 3, B). Over the next 6 months, her average blood Phe was 187 ± 143 μmol/L, a decrease of 74%. Since starting treatment, she has been able to add protein from natural sources to her diet while continuing to avoid higher-protein foods, including legumes, meat, and dairy, and while taking the Phe-free medical formula. Her growth and development have been normal, although her stature remains below the 5th percentile. There have been no reports of adverse events.

## Case 5

This girl was diagnosed with classic PKU (blood Phe, 1206 μmol/L) at 9 days of age and was started on a Phe-restricted diet. Her initial diet consisted of a Phe-free medical formula and 150-200 mg of Phe from natural sources (cow's milk or infant food). Since birth, her blood Phe level has ranged from 60 to 480 μmol/L. Although the family reported compliance with the Phe-restricted diet and maintained daily food records, they had difficulty maintaining the patient's blood Phe level within the target range of 120-360 μmol/L. Nonetheless, developmental neurocognitive testing (Battelle Developmental Inventory, Second Edition) performed at age 33 months demonstrated above-average performance.

At 3 years of age, the patient was tested for responsiveness to sapropterin. At the time testing was initiated, the patient was receiving 375 calories and 15 g of protein from medical formula and 200 mg of Phe from foods each day. Sapropterin was initiated at a dose of 300 mg (22 mg/kg/day based on a body weight of 13.8 kg). The patient's average blood Phe before starting treatment was 347 ± 174 μmol/L. Over the 2 months after starting treatment, her blood Phe level averaged 164 ± 39 μmol/L, a 53% reduction compared with the baseline average (Figure 4, A). During this testing period, she had a modest increase in Phe intake, from 175 to 225 mg/day. Over the subsequent 12 months, her blood Phe level averaged 190 ± 77 μmol/L, a 45% reduction from baseline. After the start of treatment and the drop in blood Phe level, the patient's diet has been modified to incorporate up to 1000 mg of Phe from food. Her diet includes regular pasta, cereal, and French fries. She does not eat any animal products or foods high in protein, such as legumes and nuts. When treatment was first initiated, the family reported an increased occurrence of temper tantrums. During the period of testing for responsiveness, the tantrums resolved to typical toddler behavior. No other adverse events related to treatment were reported.

## Case 6

This boy was diagnosed with mild PKU based on a blood Phe level of 150 μmol/L at 7 days of age. From birth, the patient was breast-fed, with regular infant formula supplementation and no dietary restrictions or Phe-free medical formula. At age 6 months, solid foods (cereal, fruits, vegetables) were introduced into the diet, and breast-feeding was discontinued. The family was adherent with clinic visits and blood testing. The patient developed normally, following the appropriate percentiles for growth in weight, height, and OFC. However, his blood Phe level gradually increased, ranging from 186 to 612 μmol/L. After the measurement of two successive blood Phe levels >600 μmol/L in the absence of intercurrent illness, the decision was made to initiate treatment. The options of dietary Phe restriction and testing for responsiveness to sapropterin were discussed with the parents, who preferred pharmacologic therapy.

At age 7 months, the patient was tested for responsiveness to sapropterin. He was on an unrestricted diet at the time. Sapropterin was initiated at a dose of 200 mg (20 mg/kg/day based on a weight of 8.66 kg). Within 24 hours of administration of the first dose, the patient's blood Phe level decreased by 49% and remained low for the next 10 weeks of testing, with no change in diet (Figure 4, B). During the past 14 months of therapy, his blood Phe level has remained between 60 and 138 μmol/L. Development has continued to progress normally. The only adverse event reported was diarrhea, occurring only at the initiation of treatment. This event was not sufficiently problematic to

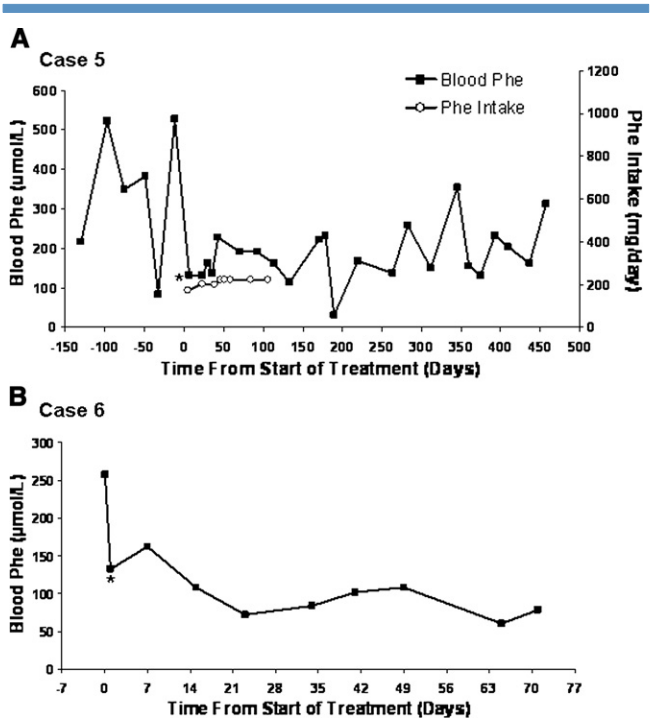


**Figure 4.** **A,** Blood Phe levels (left axis) and Phe intake (right axis) for Case 5. **B,** Blood Phe levels for Case 6. In both graphs, day 0 represents the start of sapropterin treatment.

warrant a change in treatment, and it resolved after the first 2 weeks of therapy.

## Discussion

Sapropterin appears to be relatively safe and well tolerated in the children in these case reports, including one as young as 7 months of age. The two adverse events reported in the 6 cases (temper tantrums in Case 5 and diarrhea in Case 6) resolved within the time period of testing for responsiveness. Temper tantrums, although not reported as a frequently occurring adverse event in clinical trials of sapropterin,[8-10] could be a sign of discomfort, such as related to gastrointestinal side effects, in this nonverbal patient population. Gastrointestinal-related adverse events have been associated with the initiation of sapropterin treatment, but these events usually can be alleviated by adjusting administration (ie, taking with food or formula or splitting doses), and, as in two of the reported cases, they are often self-limited and resolve without intervention.

A $BH_4$-loading protocol was originally developed in the 1970s for diagnostic purposes to distinguish between patients with PAH deficiency and those with $BH_4$ deficiency. For more than two decades, European clinics have been using this diagnostic protocol and an unregistered $BH_4$ formulation produced by Schircks Laboratory in neonates who present with an elevated blood Phe level. In addition, published studies of $BH_4$ responsiveness in patients with PKU have included subjects aged <4 years.[12-15] The $BH_4$ doses in these studies varied from 1.7 to 20 mg/kg/day, and duration of treatment ranged from 3 to 56 months. No side effects related to $BH_4$ treatment were reported for any of the patients in these studies.

In our experience, sapropterin treatment is effective in infants and young children with PKU of widely ranging severity, from those with classic PKU (Cases 1, 2, 4, and 5) to those with a milder form of the disorder (Cases 3 and 6). The therapy can benefit patients with widely ranging metabolic control, including those under good dietary control (Cases 1 and 2), those with apparently good dietary compliance but difficulty controlling blood Phe (Case 5), those with poor dietary compliance (Case 3), and those with mild PKU not previously receiving dietary therapy (Case 6). Patients with milder forms of PKU generally have a higher rate of response to sapropterin (~50%-80%) compared with those with classic PKU (~10%).[16] However, some patients with classic PKU do respond, and a response generally cannot be predicted on the basis of knowledge of the patient's mutations.

The cases reported here illustrate some of the difficulties encountered when testing for sapropterin responsiveness in young infants and children. Most infants and preschool children with PKU are well controlled on dietary therapy, and thus typically begin testing for responsiveness with a relatively low blood Phe level (as in Cases 1 and 2). In these patients, sapropterin might not produce a significant decrease in blood Phe level. In such circumstances, responsiveness can be demonstrated by increasing dietary Phe intake in a stepwise fashion while monitoring blood Phe level. Maximum dietary Phe tolerance in $BH_4$-responsive patients (determined using a well-defined, easily measured source of Phe)[17] often increases, sometimes dramatically, leading to substantial increases in natural protein intake. A carefully controlled study of dietary intake found increasing Phe tolerance with long-term $BH_4$ treatment in $BH_4$-responsive PKU patients.[14] A number of studies have demonstrated the nutritional advantages of increased consumption of natural protein.[18-24]

Patients struggling to maintain adequate metabolic control because of very low dietary Phe tolerance or difficulty adhering to a prescribed diet also can benefit from sapropterin treatment, even if additional natural protein cannot be added to the diet. In $BH_4$-responsive patients, even those with classic forms of the disease, sapropterin combined with a Phe-restricted diet can further decrease blood Phe level from that attained with diet alone (as seen in Cases 3, 4, and 5). Lower blood Phe levels in infants and young children are critical for protecting the developing brain and promoting normal neurocognitive and behavioral development.[25]

Patients with the mildest forms of PKU may have a blood Phe level below the threshold necessitating intervention early in infancy, especially if they are breast-fed. These same patients may exhibit a gradual rise in blood Phe level with increasing dietary protein intake during the first year of life. Before $BH_4$ therapy was available, the only option for these patients was to start a Phe-restricted diet, which can be more difficult when initiated later in infancy and childhood. As demonstrated by Case 6, $BH_4$ therapy may provide sufficient control of blood Phe level without the need for dietary Phe restriction and Phe-free medical food supplementation.

Another important set of issues for patients with PKU in this age group involves administration and dosing. The prescribing information for sapropterin recommends dissolving the tablets in water or apple juice. This method of administration might not be appropriate or effective for infants and some younger children, however. Subsequent studies have demonstrated that sapropterin is equally well absorbed when crushed and mixed into pudding, applesauce, and Phe-free formula.[26] Some families have had success administering sapropterin to newborns by dissolving tablets in a small volume of water and giving the solution orally with a syringe. Appropriate dosing is another important issue. As seen in these cases, clinics take different approaches to dosing. Some clinics start patients at 20 mg/kg/day (Cases 1, 2, 5, and 6) and reduce the dose only if the patient maintains a very low blood Phe level (eg, <60 $\mu$mol/L). Other clinics (Cases 3 and 4) start at a dose of 10 mg/kg/day and increase the dose if better blood Phe control is desired. In Cases 3 and 4, the higher dose of 20 mg/kg/day led to a further decrease in blood Phe level with improved metabolic control.

In conclusion, given the increasing evidence that maintaining blood Phe levels below 360 $\mu$mol/L is important for the normal development of neurocognitive and behavioral

function, sapropterin can be combined with the Phe-restricted diet to control blood Phe levels in young patients responsive to sapropterin therapy. ■

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