

New era in treatment for phenylketonuria: Pharmacologic therapy with sapropterin dihydrochloride

Cary O Harding

Departments of Molecular and
Medical Genetics and Pediatrics,
Oregon Health & Science
University, Portland, Oregon, USA

Abstract: Oral administration of sapropterin hydrochloride, recently approved for use by the US Food and Drug Administration and the European Commission, is a novel approach for the treatment of phenylketonuria (PKU), one of the most common inborn errors of metabolism. PKU is caused by an inherited deficiency of the enzyme phenylalanine hydroxylase (PAH), and the pathophysiology of the disorder is related to chronic accumulation of the free amino acid phenylalanine in tissues. Contemporary therapy is based upon restriction of dietary protein intake, which leads to reduction of blood phenylalanine levels. This therapy is difficult to maintain throughout life, and dietary noncompliance is commonplace. Sapropterin dihydrochloride is a synthetic version of tetrahydrobiopterin, the naturally occurring pterin cofactor that is required for PAH-mediated phenylalanine hydroxylation. In a subset of individuals with PAH deficiency, sapropterin administration leads to reduction in blood phenylalanine levels independent of dietary protein. For these individuals, sapropterin is an effective novel therapy for PKU.

Keywords: sapropterin dihydrochloride, phenylketonuria, phenylalanine, tetrahydrobiopterin

Introduction

Dietary restriction of phenylalanine intake has been the mainstay of therapy for phenylketonuria (PKU), one of the most common inborn errors of metabolism, for the past 50 years. With the recent US Food and Drug Administration (FDA) and European Commission approvals of sapropterin dihydrochloride (Kuvan[®], BioMarin Corporation, Tiburon, CA), a new era in PKU treatment has begun. Sapropterin dihydrochloride is a synthetic version of the naturally occurring pterin cofactor, tetrahydrobiopterin (BH₄). In a subset of individuals with PKU, sapropterin treatment substantially reduces blood phenylalanine levels independent of dietary phenylalanine intake. For these so-called “BH₄-responsive” patients, sapropterin therapy provides the benefit of improved disease control and may even eliminate the need for dietary therapy completely in individuals with milder forms of hyperphenylalaninemia.

Biology of phenylketonuria and tetrahydrobiopterin

PKU has an annual incidence of about 1:16,000 births in the US.¹ PKU is caused by recessively inherited mutations in the *PAH* gene that encodes the enzyme phenylalanine hydroxylase (PAH). PAH is predominantly expressed in liver (but also kidney and pancreas) and catalyzes the irreversible hydroxylation of phenylalanine, an essential amino acid, to tyrosine (Figure 1). PAH is a homotetramer that requires iron and molecular oxygen as well as the unconjugated pterin cofactor, BH₄, for catalytic activity.

Correspondence: Cary O Harding
OHSU, Mailstop L-103, 3181 Sam Jackson
Park Rd, Portland, OR 97239, USA
Tel +1 503 494 7608
Fax +1 503 494 6886
Email hardingc@ohsu.edu

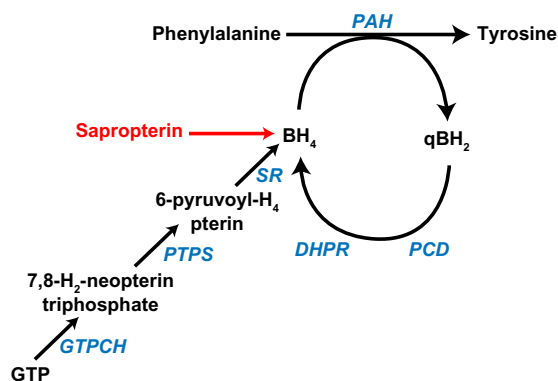


Figure 1 Phenylalanine hydroxylation. Phenylalanine is hydroxylated to tyrosine through the catalytic activity of phenylalanine hydroxylase, which requires the presence of the unconjugated pterin cofactor, tetrahydrobiopterin (BH_4). Sapropterin is a synthetic form of BH_4 that augments the endogenous BH_4 supply. During phenylalanine hydroxylation, BH_4 is oxidized to quinonoid dihydrobiopterin (qBH_2). Fully active BH_4 is regenerated through the sequential action of pterin-4a-carbinolamine dehydratase and dihydropteridine reductase (DHPR) or may be synthesized *de novo* from guanosine triphosphate (GTP).²

BH_4 is synthesized *de novo* from guanosine triphosphate in several tissues, including liver, but is also recycled after phenylalanine hydroxylation through enzymatically-catalyzed reduction.² Inherited deficiency of BH_4 synthesis or recycling enzymes is the cause of hyperphenylalaninemia in approximately 2% of infants detected through newborn screening. Treatment of these children frequently requires chronic oral or parenteral BH_4 administration in addition to dietary phenylalanine restriction.

PAH deficiency leads to accumulation of phenylalanine in all tissues of the body and relative deficiency of tyrosine. Untreated PKU is associated with chronic hyperphenylalaninemia, microcephaly, mental retardation, epilepsy, relative hypopigmentation, growth delay, and eczema. Fortunately, all infants in the US and most Western countries are screened for hyperphenylalaninemia at 24–72 hours of life. Initiation of therapy early in life prevents the major manifestations of the disease. Contemporary therapy is based upon the restriction of dietary phenylalanine intake through the reduction of dietary protein. Under this regimen, synthetic medical foods must be consumed in order to provide adequate intake of total energy and amino acids other than phenylalanine. Intellectual outcome is directly related to success in reducing blood phenylalanine levels,³ and restriction of dietary phenylalanine is recommended throughout the life of the individual with PKU.⁴ However, this therapeutic approach is complicated, unpalatable, and difficult to maintain through adolescence and into adulthood. Loss of dietary control may be associated with deterioration of cognitive performance and attention span, resulting from development of a neurodegenerative disease of white matter,⁵ and in pregnant women with PKU and elevated blood phenylalanine, severe teratogenesis with

fetal growth failure, microcephaly, mental retardation, and congenital heart disease, ie, the so-called maternal PKU syndrome.⁶ For all of these reasons, novel alternatives to dietary therapy are being sought.

History of tetrahydrobiopterin responsiveness in phenylketonuria

Individuals with inherited PAH deficiency have normal biopterin content in blood and urine, but Kure et al reported that oral administration of additional BH_4 to some individuals with mild hyperphenylalaninemia led to a significant reduction in blood phenylalanine levels without altering dietary phenylalanine content.⁷ Several other investigators have subsequently confirmed this observation.^{8–17} The basis of BH_4 responsiveness may be related to different molecular mechanisms. Increased liver BH_4 content may simply stimulate the activity of mutant partially active PAH enzyme¹⁸ or it may act as a chemical chaperone to stabilize mutant PAH monomers.¹⁹ Proof of this latter mechanism is provided by investigation of other small molecules that act as chaperones to stabilize mutant PAH.²⁰ Some specific PAH mutations are known to affect the affinity of the PAH enzyme for its biopterin cofactor.²¹ In patients with these specific mutations, oral biopterin administration may overcome this block and restore enzymatic activity. In reality, only a few such mutations have been shown to be often (but not invariably) associated with BH_4 responsiveness in PKU patients^{22,23} while other mutations, such as the R408W mutation, are consistently associated with nonresponsiveness. BH_4 responsiveness in an individual PKU patient cannot always be accurately predicted from their PAH genotype.^{22,24}

Clinical trials of sapropterin in phenylketonuria

After the discovery that some PKU patients could benefit from BH_4 supplementation, few patients were able to avail themselves of this treatment option because the worldwide supply of BH_4 was limited and detailed pharmacokinetic studies had not been performed. In the USA, BH_4 was approved by the FDA only for use as an investigational drug. To overcome this problem, BioMarin Corporation (Novato, CA) initiated a specific effort to develop and intensively study sapropterin dihydrochloride ((6R)-2-amino-6-[(1R, 2S)-1,2-dihydroxypropyl]-5,6,7,8-tetrahydro-4(3H)-pteridinone dihydrochloride, Figure 2), a biologically active synthetic form of BH_4 , in subjects with PKU. Sapropterin dihydrochloride is supplied in airtight blister packs as 100 mg tablets that may be administered whole or dissolved in water or apple juice. The tablets contain ascorbic acid to maintain

In a third clinical trial, 80 sapropterin-responsive subjects participated in a multicenter, open-label extension study.²⁹ The initial phase of the trial was a forced dose titration study, with subjects receiving doses of 5, 20, and 10 mg/kg/day of sapropterin consecutively for two weeks each. This was followed by a four-week period of 10 mg/kg/day and then a 12-week fixed dose extension. In the last phase, subjects received one of three different sapropterin doses (5, 10, or 20 mg/kg/day) based upon their individual responses in the dose titration phase of the study. In the first phase, although plasma phenylalanine levels decreased from week 0 at all sapropterin doses, a dose-response relationship was demonstrated, with significantly lower plasma phenylalanine levels on average during treatment with 10 or 20 mg/kg/day than when the subjects received only 5 mg/kg/day. During the fixed-dose extension phase, six subjects (8%) responded to 5 mg/kg/day, while 37 subjects (46%) received 10 mg/kg/day, and 37 subjects (46%) received 20 mg/kg/day. The choice of dose and the reduction in phenylalanine levels achieved by 22 weeks clearly reflect a dichotomy in the severity of PKU in the study subjects. Individuals with higher phenylalanine levels at baseline required more drug to effect a decrease in blood phenylalanine, and the drop in phenylalanine level achieved was not as satisfactory as that demonstrated by subjects responding to either 5 or 10 mg/kg/day. Overall, plasma phenylalanine decreased by 190.5 μM (± 355.7) in all dose groups after 22 weeks of drug. The mean plasma phenylalanine level at the end of 22 weeks in the 20 mg/kg dose group was 895.7 (± 407.2) μM while mean phenylalanine levels in the 5 and 10 mg/kg dose groups were 437.8 (± 260.5) μM and 449.9 (± 193.1) μM , respectively. Individuals with a lower baseline phenylalanine level (a measure of dietary phenylalanine tolerance) showed greater responsiveness to the drug. Only 50%, 49%, and 42% of subjects in the 5, 10, and 20 mg/kg dose groups, respectively, achieved a 30% decrease in plasma phenylalanine from baseline at the end of the 22 weeks. Recall that all study subjects had demonstrated a 30% reduction in plasma phenylalanine over eight days in the initial screening study. Unintended changes in dietary protein intake over the course of the trials (further protein restriction during the screening trial or liberalization of dietary protein intake during the extension trial) would have affected these results. There were no minor or severe adverse events attributable to sapropterin treatment in the trial. This extension study demonstrates that sapropterin treatment may safely reduce plasma phenylalanine concentrations in a dose-dependent manner in BH_4 -responsive individuals. Furthermore, empiric use of the drug for one month or more may be needed.

The effectiveness of sapropterin treatment has also been examined in 90 children aged 4–12 years with PKU while they continued on a protein-restricted diet.³⁰ Of these subjects, 56% experienced a 30% reduction in blood phenylalanine levels after eight days of sapropterin treatment. After the challenge period, all responders were offered participation in a placebo-controlled trial during which dietary phenylalanine intake was gradually increased. In the group receiving sapropterin, dietary phenylalanine tolerance doubled on average, with no significant increase in blood phenylalanine levels in comparison with phenylalanine tolerance prior to sapropterin treatment, while dietary phenylalanine tolerance increased only slightly in the placebo group. Again, no significant safety issues were revealed.

Based on the accumulated study data, the FDA approved sapropterin dihydrochloride for clinical use in December 2007. Marketing authorization for sapropterin has subsequently been granted in Japan (July 2008) and Europe (December 2008), and is under expedited review in Canada. In Europe, sapropterin has been licensed for use in children with PAH deficiency over the age of four years, and also in individuals of all ages with hyperphenylalaninemia due to congenital BH_4 deficiency. In the US, sapropterin treatment is approved in all age groups and in pregnant women, even though sapropterin has not been formally studied in children under four years age or during pregnancy. Limited experience with administration of other commercially available forms of BH_4 during pregnancy suggests that no adverse effects are to be expected.³¹ In the case of the pregnant woman with BH_4 -responsive PKU, the well documented risks to the fetus associated with maternal hyperphenylalaninemia likely outweigh any putative risks of sapropterin treatment. Still, these issues deserve further study and BioMarin has initiated a voluntary registry system to accumulate data on the use of sapropterin in young children and during pregnancy.

Post-approval clinical use of sapropterin

Now that sapropterin has gained FDA approval, the task ahead is to determine which PKU patients will benefit most from this novel therapeutic approach and how to best introduce this medication into a specific patient's dietary treatment regimen. Sapropterin has been formally proven in research studies to lower blood phenylalanine levels in individuals who are responsive, but limited data are available concerning the effect of sapropterin treatment on actual protein tolerance. Can the sapropterin-treated patient safely increase their dietary protein intake and maintain blood phenylalanine levels within a designated treatment range? Also, long-term safety and cognitive

outcomes should be evaluated in patients who will probably be treated with sapropterin for many years.

The determination of whether a specific patient with PKU is truly BH_4 -responsive is clearly key to the decision about adding sapropterin to the patient's treatment regimen. To some degree, the definition of "responsiveness" is an arbitrary one. For the purposes of the screening study, responsiveness was defined as a 30% decrease in plasma phenylalanine after an eight-day trial of oral sapropterin at 10 mg/kg/day. As we have seen, subsequent evaluations have revealed both false-positive and false-negative results from this screening procedure. Some individuals who met criteria for responsiveness during the screening trial subsequently did not maintain a therapeutic effect from sapropterin over the longer term. Some individuals who did not meet criteria for responsiveness with a sapropterin dose of 10 mg/kg/day were later found to be responsive to the higher dose of 20 mg/kg/day. It has been suggested that BH_4 responsiveness would require a patient with PKU to carry at least one *PAH* mutant allele that allows for residual enzyme activity.¹⁸ However, in the clinical trial, a few individuals who were found to be sapropterin-responsive carried *PAH* mutations that were predicted to yield severe *PAH* deficiency. A recent comprehensive review suggests that genotype can predict to some degree whether a patient with PKU will be responsive to BH_4 , but that ultimately only BH_4 challenge will fully ascertain BH_4 responsiveness.²⁴

In addition to the eight-day screening trial employed in the clinical trial,²⁷ several other BH_4 challenge protocols have been described in the literature, and these have recommended differing BH_4 doses, different durations of challenge, determination of blood phenylalanine levels at different times, varying percentage reductions in blood phenylalanine required to define BH_4 responsiveness and, in some cases, challenging the subject with a standardized amount of dietary phenylalanine along with BH_4 . This topic has been reviewed.³² Recent published data have revealed that the decrease in blood phenylalanine following a single BH_4 dose obeys a first-order kinetic model only over the first eight hours after BH_4 administration.³³ Accordingly, a single BH_4 loading test (20 mg/kg) with monitoring of blood phenylalanine at 0, 8, 12, and 24 hours has been proposed as an evaluation of responsiveness.³⁴ If blood phenylalanine dropped more than 20% in the short term, then a several-week trial with BH_4 dose adjustment to maintain optimal phenylalanine levels would be warranted.

A rational algorithm for testing BH_4 responsiveness in a routine clinical setting has been proposed³⁵ and a similar protocol has been endorsed by clinicians in Europe.³⁶ This algorithm evaluates both the short-term response to BH_4

administration (allowing for upward adjustment of dietary phenylalanine intake if blood phenylalanine levels fall dramatically after BH_4 treatment) and the longer-term efficacy of sapropterin treatment. In this algorithm, blood phenylalanine is measured prior to sapropterin administration and on days 1, 7, 14, and 28 days following sapropterin 20 mg/kg/day. The sapropterin dose may be decreased or dietary phenylalanine increased if blood phenylalanine levels decrease below the target range. Responsiveness is not defined by any specific percentage decrease in phenylalanine but rather by whether the decrease in phenylalanine is thought by the clinician and patient to be clinically meaningful. Continued sapropterin treatment is warranted if blood phenylalanine levels are lowered into a specific target range defined by clinician and patient and is particularly relevant if dietary phenylalanine restriction can be relaxed without increasing blood phenylalanine. This testing algorithm allows for the individualization of therapy and flexibility in the assessment of BH_4 responsiveness.

Cost of sapropterin

The cost of sapropterin therapy versus the PKU diet must also be considered. As a drug with an orphan product designation, the costs of drug development for sapropterin are distributed among a relatively small patient population. The cost of daily sapropterin therapy at the highest dose of 20 mg/kg/day is US \$100,000 to \$150,000 for the average adult patient versus the cost of the phenylalanine-restricted diet, including the use of medical foods, which is typically US \$15,000 to \$20,000 per year. The PKU patient and their clinician must consider these factors when deciding whether to employ sapropterin therapy.

Conclusions

The systematic evaluation of sapropterin responsiveness in a PKU population and the subsequent commercial availability of a validated form of BH_4 have now provided a new therapeutic option for phenylketonuria. As discussed, continuance of strict dietary therapy throughout life is recommended but is practically difficult. Compliance with this recommendation in adults is often poor. For a subset of individuals with PKU, sapropterin will be essential as sole therapy. For other patients, sapropterin treatment may not completely eliminate the need for dietary therapy, but may increase a patient's dietary protein tolerance, allowing a significant improvement in daily quality of life. The introduction of sapropterin for widespread clinical use represents an exciting time in the evolution of therapy for PKU.

Disclosure

The author reports no conflict of interest in this work.

References

- Donlon J, Levy H, Scriver CR. Hyperphenylalaninemia: Phenylalanine hydroxylase deficiency. In: Valle D, Beaudet AL, Vogelstein B, editors. *The Metabolic and Molecular Bases of Inherited Disease*. New York, NY: McGraw-Hill; 2008.
- Thony B, Auerbach G, Blau N. Tetrahydrobiopterin biosynthesis, regeneration and functions. *Biochem J*. 2000;347(Pt 1):1–16.
- Azen CG, Koch R, Friedman EG, et al. Intellectual development in 12-year-old children treated for phenylketonuria. *Am J Dis Child*. 1991; 145(1):35–39.
- National Institutes of Health Consensus Development Conference Statement: Phenylketonuria: Screening and management, 2000 Oct 16–18. *Pediatrics*. 2001;108(4):972–982.
- Thompson AJ, Smith I, Brenton T, et al. Neurological deterioration in young adults with phenylketonuria. *Lancet*. 1990;336(8720): 602–605.
- Platt LD, Koch R, Hanley WB, et al. The international study of pregnancy outcome in women with maternal phenylketonuria: Report of a 12-year study. *Am J Obstet Gynecol*. 2000;182(2):326–333.
- Kure S, Hou DC, Ohura T, et al. Tetrahydrobiopterin-responsive phenylalanine hydroxylase deficiency. *J Pediatr*. 1999;135(3):375–378.
- Lindner M, Haas D, Mayatepek E, Zschocke J, Burgard P. Tetrahydrobiopterin responsiveness in phenylketonuria differs between patients with the same genotype. *Mol Genet Metab*. 2001;73(1):104–106.
- Bernegger C, Blau N. High frequency of tetrahydrobiopterin responsiveness among hyperphenylalaninemias: A study of 1,919 patients observed from 1988 to 2002. *Mol Genet Metab*. 2002;77(4):304–313.
- Muntau AC, Roschinger W, Habich M, et al. Tetrahydrobiopterin as an alternative treatment for mild phenylketonuria. *N Engl J Med*. 2002;347(26):2122–2132.
- Cerone R, Schiaffino MC, Fantasia AR, et al. Long-term follow-up of a patient with mild tetrahydrobiopterin-responsive phenylketonuria. *Mol Genet Metab*. 2004;81(2):137–139.
- Shintaku H, Kure S, Ohura T, et al. Long-term treatment and diagnosis of tetrahydrobiopterin-responsive hyperphenylalaninemia with a mutant phenylalanine hydroxylase gene. *Pediatr Res*. 2004;55(3): 425–430.
- Fiege B, Bonafe L, Balhausen D, et al. Extended tetrahydrobiopterin loading test in the diagnosis of cofactor-responsive phenylketonuria: A pilot study. *Mol Genet Metab*. 2005;86 Suppl 1:S91–S95.
- Fiori L, Fiege B, Riva E, Giovannini M. Incidence of BH₄-responsiveness in phenylalanine-hydroxylase-deficient Italian patients. *Mol Genet Metab*. 2005;86 Suppl 1:S67–S74.
- Hennermann JB, Bühner C, Blau N, Vetter B, Mönch E. Long-term treatment with tetrahydrobiopterin increases phenylalanine tolerance in children with severe phenotype of phenylketonuria. *Mol Genet Metab*. 2005;86 Suppl 1:S86–S90.
- Matalon R, Michals-Matalon K, Koch R, Grady J, Tying S, Stevens RC. Response of patients with phenylketonuria in the US to tetrahydrobiopterin. *Mol Genet Metab*. 2005;86 Suppl 1:S17–S21.
- Mitchell JJ, Wilcken B, Alexander I, et al. Tetrahydrobiopterin-responsive phenylketonuria: The New South Wales experience. *Mol Genet Metab*. 2005;86 Suppl 1:S81–S85.
- Blau N, Erlandsen H. The metabolic and molecular bases of tetrahydrobiopterin-responsive phenylalanine hydroxylase deficiency. *Mol Genet Metab*. 2004;82(2):101–111.
- Dobrowolski SF, Pey AL, Koch R, et al. Biochemical characterization of mutant phenylalanine hydroxylase enzymes and correlation with clinical presentation in hyperphenylalaninaemic patients. *J Inherit Metab Dis*. 2009;32(1):10–21.
- Pey AL, Ying M, Cremades N, et al. Identification of pharmacological chaperones as potential therapeutic agents to treat phenylketonuria. *J Clin Invest*. 2008;118(8):2858–2867.
- Erlandsen H, Pey AL, Gamez A, et al. Correction of kinetic and stability defects by tetrahydrobiopterin in phenylketonuria patients with certain phenylalanine hydroxylase mutations. *Proc Natl Acad Sci U S A*. 2004;101(48):16903–16908.
- Karacic I, Meili D, Sarnavka V, et al. Genotype-predicted tetrahydrobiopterin (BH₄)-responsiveness and molecular genetics in Croatian patients with phenylalanine hydroxylase (PAH) deficiency. *Mol Genet Metab*. 2009;97(3):165–171.
- Trefz FK, Scheible D, Götz H, Frauendienst-Egger G. Significance of genotype in tetrahydrobiopterin-responsive phenylketonuria. *J Inherit Metab Dis*. 2009;32(1):22–26.
- Zurfluh MR, Zschocke J, Lindner M, et al. Molecular genetics of tetrahydrobiopterin-responsive phenylalanine hydroxylase deficiency. *Hum Mutat*. 2008;29(1):167–175.
- Feillet F, Clarke L, Meli C, et al. Pharmacokinetics of sapropterin in patients with phenylketonuria. *Clin Pharmacokinet*. 2008;47(12):817–825.
- Harding CO, Neff M, Wild K, et al. The fate of intravenously administered tetrahydrobiopterin and its implications for heterologous gene therapy of phenylketonuria. *Mol Genet Metab*. 2004;81(1):52–57.
- Burton BK, Grange DK, Milanowski A, et al. The response of patients with phenylketonuria and elevated serum phenylalanine to treatment with oral sapropterin dihydrochloride (6R-tetrahydrobiopterin): A phase II, multicentre, open-label, screening study. *J Inherit Metab Dis*. 2007;30(5):700–707.
- Levy HL, Milanowski A, Chakrapani A, et al. Efficacy of sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH₄) for reduction of phenylalanine concentration in patients with phenylketonuria: A phase III randomised placebo-controlled study. *Lancet*. 2007;370(9586):504–510.
- Lee P, Treacy EP, Crombez E, et al. Safety and efficacy of 22 weeks of treatment with sapropterin dihydrochloride in patients with phenylketonuria. *Am J Med Genet A*. 2008;146A(22):2851–2859.
- Trefz FK, Burton BK, Longo N, et al. Efficacy of sapropterin dihydrochloride in increasing phenylalanine tolerance in children with phenylketonuria: A phase III, randomized, double-blind, placebo-controlled study. *J Pediatr*. 2009;154(5):700–707.
- Koch R, Moseley K, Guttler F. Tetrahydrobiopterin and maternal PKU. *Mol Genet Metab*. 2005;86 Suppl 1:S139–S141.
- Fiege B, Blau N. Assessment of tetrahydrobiopterin (BH₄) responsiveness in phenylketonuria. *J Pediatr*. 2007;150(6):627–630.
- Langenbeck U. Classifying tetrahydrobiopterin responsiveness in the hyperphenylalaninaemias. *J Inherit Metab Dis*. 2008;31(1):67–72.
- Blau N. Defining tetrahydrobiopterin (BH₄)-responsiveness in PKU. *J Inherit Metab Dis*. 2008;31(1):2–3.
- Levy H, Burton B, Cederbaum S, Scriver C. Recommendations for evaluation of responsiveness to tetrahydrobiopterin (BH₄) in phenylketonuria and its use in treatment. *Mol Genet Metab*. 2007;92(4):287–291.
- Blau N, Belanger-Quintana A, Demirkol M, et al. Optimizing the use of sapropterin (BH₄) in the management of phenylketonuria. *Mol Genet Metab*. 2009;96(4):158–163.

Biologics: Targets & Therapy

Publish your work in this journal

Biologics: Targets & Therapy is an international, peer-reviewed journal focusing on the patho-physiological rationale for and clinical application of Biologic agents in the management of autoimmune diseases, cancers or other pathologies where a molecular target can be identified. This journal is indexed on PubMed Central, CAS, EMBase, Scopus

Submit your manuscript here: <http://www.dovepress.com/biologics-targets--therapy-journal>

Dovepress

and the Elsevier Bibliographic databases. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.