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New Drug Evaluation: Saproterin for Phenylketonuria

Month/Year of Review: May 2013
New drug(s): Saproterin (Kuvan®)
End date of literature search: March 2013

Date of Last Review: None
Manufacturer: BioMarin Pharmaceutical Inc.

Research Questions:

- What is the evidence saproterin is effective for treatment of phenylketonuria (PKU)?
- What is the evidence saproterin is safe for treatment of phenylketonuria (PKU)?
- Are there subgroups of patients where saproterin may be more effective or safer?

Conclusions:

- There is moderate level of evidence that saproterin can lower the blood phenylalanine (Phe) levels in some patients with PKU in short term (up to 10 weeks)[1,2]. It is unclear whether the patients whose Phe levels go down will also show clinical outcomes such as improvements in their health, well-being, and neurocognitive function.
- There are no serious adverse events associated with the treatment in short term.
- There is insufficient evidence on the long-term effects of saproterin and no clear evidence of effectiveness in severe PKU.
- There is insufficient evidence on how to identify the type of patients most likely to benefit because there is no standardized clinical protocol to select potential patients who might be responsive to saproterin treatment.

Recommendations:

- Implement saproterin prior authorization criteria due to lack of long term data and clinical significance outcomes data to support deceased blood Phe level associated with improved neurocognitive and/or psychosocial functions. (Appendix 3)
- In light of lack of national treatment consensus, recommend working with metabolic clinic providers in the region to formulate a uniform and practical treatment protocol for managing patients with PKU including the use of saproterin for patients who are likely to respond.
- Recommend saproterin be considered for the “High Cost Marginal Benefit” policy.

Reason for Review:

Saproterin is the only Food and Drug Administration (FDA) approved therapeutic agent for treatment of PKU in conjunction with a Phe-restricted diet. The major benefit appears to be a modest liberation of a phenylalanine-restricted diet, however, its use does not allow complete discontinuation of a restricted diet and not all patients with PKU will respond to the therapy. This review will examine the place in therapy for saproterin including appropriate patient selection for treatment, monitoring parameters for response and long term treatment, and identify relevant comparative effectiveness evidence, high-quality systematic reviews, or evidence-based guidelines for consideration.

Background:

Phenylketonuria (PKU) is a disorder affecting the aromatic amino acid phenylalanine resulted from a deficiency of phenylalanine hydroxylase (PAH). If left untreated, PKU can lead to profound mental retardation, seizures, behavioral problems and other symptoms.[3,4] It is a form of rare inborn error in amino acid metabolism. The incidence of PKU is approximately 1 in 13,500 to 19,000 births in the US.[5] The hepatic enzyme PAH catalyzes the conversion of the essential amino acid phenylalanine to tyrosine. Tetrahydrobiopterine (BH4) is a cofactor required for PAH activity.[6] Due to deficiency in PAH, individuals with PKU have an over abundance of phenylalanine, which plays an integral role in the development of normal brain function. Although the mechanism by which the elevated concentration of phenylalanine causes intellectual disability is unknown, excessive phenylalanine is thought to interfere with brain growth, myelination and neurotransmitter synthesis. Because of widespread neonatal screening, overt clinical manifestations of PKU are rare. In the U.S, the screening typically occurs at 24-48 hours after birth.[7]

Cognitive outcome appears to be correlated with the extent of control of blood phenylalanine concentration, especially during early childhood. However, the blood phenylalanine concentration associated with optimal neuro-developmental outcome is uncertain. No consensus exists among treatment centers in the United States or other countries. The National Institutes of Health Consensus Development Conference on PKU recommended maintaining a blood concentration of 2 to 6 mg/dL (120 to 360 µmol/L) for affected children through 12 years of age and 2 to 15 mg/dL (120 to 900 µmol/L) after 12 years of age. However, although data are limited, higher blood phenylalanine concentrations appear to adversely affect brain function, even in adults. Thus, maintenance of lower levels (2 to 10 mg/dL, 120 to 600 µmol/L) is strongly encouraged during adolescence or even beyond.[8]

The mainstay of therapy in PKU is dietary restriction of phenylalanine. Dietary treatment appears to reverse all signs of PKU except cognitive impairment that has already occurred. The PKU diet consists of a restriction of dietary protein in order to minimize phenylalanine (Phe) intake. It requires supplementation with special medical formulas that supply sufficient essential amino acids, energy, vitamins and minerals. The diet should be started in the first weeks of age and maintained for life.[9] Since the dietary management of PKU was established 60 years ago,[10] the knowledge of the generic basis of disease and enzymology has allowed for the investigation of novel pharmacologic therapies to directly ameliorate the effects of a mutant enzyme.[9] Saproterin is a synthetic formulation of BH4, which is FDA-approved to reduce blood Phe concentrations in patients with hyperphenylalaninemia due to BH4-responsive PKU. The clinical trials demonstrated saproterin can lower the blood Phe levels in some patients with PKU. However, there are no sufficient details on how to identify the type of patients that would get improvements. There are different definitions of responses ranging from a 20% to 50% reduction in blood Phe levels.[11] Saproterin responsiveness in clinical trials was defined as ≥ 30% blood Phe levels reductions, but this definition is arbitrary and many clinicians consider a 20% reduction in Phe clinically beneficial.

Methods:
A Medline (Ovid) literature search was conducted in the past 10 years for new randomized controlled trials (RCT's) and controlled clinical trials comparing medications head-to-head in the treatment of PKU using saproterin/kuvan®, and limits for humans, English language. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
Cochrane Collaboration[12]
In October 2012, Somaraju et al. conducted a systematic review to assess the safety and efficacy of saproterin in lowering blood phenylalanine concentration in people with PKU. Two placebo-controlled trials were included.[1,2] One trial administered 10mg/kg/day saproterin in 89 children and adults with phenylketonuria whose diets were not restricted and who had previously responded to saproterin. This trial measured change in blood phenylalanine concentration. The second trial screened 90 children (4 to 12 years) with phenylketonuria whose diet was restricted, for responsiveness to saproterin. Forty-six responders entered the placebo-controlled part of the trial and received 20 mg/kg/day saproterin. This trial measured change in both phenylalanine concentration and protein tolerance. Both trials reported adverse events. The trials showed an overall low risk of bias; but both were BioMarin-sponsored. One trial showed a significant lowering in blood phenylalanine concentration in the saproterin group (10 mg/kg/day), mean difference -238.80 µmol/L (95% confidence interval -343.09 to -134.51); a second trial (20 mg/kg/day saproterin) showed a non-significant difference, mean difference -51.90 µmol/L (95%confidence interval -197.27 to 93.47). The second trial also reported a significant increase in supplemental phenylalanine tolerated, mean difference 18.00 mg/kg/day (95% confidence interval 12.28 to 23.72) in the 20 mg/kg/day saproterin group. The authors concluded that there is evidence of short-term benefit from using saproterin in some patients with saproterin-responsive forms of phenylketonuria; blood phenylalanine concentration is lowered and protein tolerance increased. There are no serious adverse events associated with using saproterin in the short term. There is no evidence on the long-term effects of saproterin and no clear evidence of effectiveness in severe phenylketonuria.

CADTH Recommendation[13]
In 2011 the Canadian Exert Drug Advisory Committee (CEDAC), subcommittee of CADTH concluded that there was not enough information to identify the type of individuals with PKU for whom saproterin would provide enough improvement to be cost effective based on the clinical and pharmacoeconomic evidence available up to date. The committee acknowledges that saproterin can lower the Phe levels in the blood of some patients with PKU. In addition, it is not clear whether the patients whose Phe levels go down will also show important improvements in their health and well-being. The committee recommends that saproterin not be listed by Canada's publicly funded drug plans for the treatment of PKU.

Recommendations for Determining Response to Saproterin and its use in Patients with PKU
Clinicians in the field have attempted to develop a uniform and practical approach to the use of saproterin for treating PKU in conjunctions with diet although a national consensus is still lacking. Summary of relevant recommendations developed by these experts are listed below.

Selected Relevant Recommendations by Levy H et al (2007)[14]

Patient selection for saproterin responsiveness in order of preference:

- Young patients on diet but not in optimal phenylalanine control
- Patients with mild PKU based on dietary phenylalanine tolerance and initial confirmatory blood phenylalanine concentration, as those are the most likely to respond.
- All other patients with PKU, beginning with younger patients on diet, then older patients struggling with diet or not on diet (but experiencing psychological difficulties), and finally, all patients not yet tested.

Regimen for saproterin responsiveness:

- The initial test dose of should be 20mg/kg daily. The dose may be titrated between 5 and 20mg/kg/day to achieve the desired results and based on tolerability.
- Before the first dose, a blood specimen for phenylalanine determination must be collected. There should be no change in diet. Subsequent specimens for phenylalanine determination should be collected on day 1,7,14 and 28. The blood should be collected at the same time of day for each patient.

Determination of responsiveness:

- The most widely accepted standard of response to BH4 is a ≥ 30% reduction in blood phenylalanine level. The authors recognize that a lower degree of responsiveness, e.g. 20% might also be considered sufficient in some individual circumstances.

Optimized Protocol by Blau N et al (2009)[15]

The FDA approved algorithm for initiating therapy with saproterin recommends that a measurement of blood Phe is followed by an initial daily dose of saproterin at 10mg/kg/day for one week, at the end of which a repeat blood Phe measurement is taken. If a sufficient reduction in blood Phe level is observed, the dose can be increased to 20mg/day, and blood Phe levels are followed for a total initial treatment period of up to one month. At this time, treatment is stopped for non-responders, while responders entered a dose optimization phase when the dose of saproterin is adjusted based on blood Phe level. Because the initial trial phase is one month, potentially it may create false positive and false negative if patients adjust their diet during trial phase. In 2009 the European working group on PKU proposed an optimized protocol. The protocol suggests administration of single dose of saproterin at 20mg/kg followed by serial measurement of blood Phe during the first 24 hours to determine the initial responders defined as greater than 30% reduction of blood Phe level, and to do a second 24-h test later after second dose on second day for patients who showed a rather slower responsiveness in the first test. After 48 hours responders will enter a dose titration phase.

Recommendations for the use of saproterin in PKU by Cunningham a et al. (2012)[16]

In 2011 a group of metabolic dieticians who practice in various clinics across the North American in conjunction with physicians with extensive experience in PKU management developed the recommendations in patient selection and determination of saproterin response to the long-term management of patients on saproterin therapy. Target Phe levels, nutritional adequacy, neurocognitive screening and adherence to treatment are addressed to optimize patient outcomes.

Key recommendations:

Patient Selection:

- A trial of saproterin may be offered to all patients with PKU to determine clinical benefit. Patients should be evaluated to ensure their ability to adhere to the treatment protocol over the 1-2 month trial period.

- Special consideration is warranted for the following patient population: patient with mild PKU; infants and young children; pregnant women and late-treated and untreated adults.

Baseline Assessment:

- Blood Phe concentration: ideally 3 or more blood Phe levels within the month prior to the start of the trial.
- Concurrent medications, supplements assessment and mental health screening

Implementation of saproterin and monitoring during a trial phase:

- An initial dose of 20mg/kg/day is recommended. The dose may be titrated between 5 and 20mg/kg/day
- Blood Phe level should be performed prior to initiation of treatment and weekly thereafter until completion of the trial. For infants and young children, a blood Phe test is best obtained at day 1 or 2 of the trial. Blood sample should be obtained at a consistent time of the day that is at least 2 hours after food intake.
- Patients should be instructed not to make any lifestyle changes and maintain their usual diet.

Determination of clinical benefit of saproterin:

1) Reduced blood Phe levels: Although in clinical trials, a ≥ 30% decrease in blood Phe concentration was used to define saproterin response, a smaller reduction may be clinical meaningful if accompanied with an increase in dietary Phe tolerance and/or an improvement in neurocognitive/psychosocial functioning.
2) Increased dietary Phe tolerance
3) Improved neurocognitive and/or psychosocial functioning
4) Improved blood Phe stability

New Drug Evaluation:

FDA approved indications:

Saproterin (Kuvan®) was FDA approved to reduce blood Phe levels in patients with hyperphenylalaninemia (HPA) due to BH4-responsive PKU in conjunction with a Phe-restricted diet.

Clinical Efficacy Data:

There were two double blind, placebo controlled studies evaluated the efficacy and safety of saproterin in patients with PKU.[1,2] The first randomized clinical trial by Levy et al.[1] was a phase III, multicenter, randomized, double-blind, placebo controlled trial, that included 88 patients who received at least one dose of study drug. There were 41 patients in treatment group received oral doses of saproterin 10mg/kg and 47 patients received placebo once daily for 6 weeks. The patients enrolled in this study were pediatric and adult patients who were screened to show responsiveness, defined as a reduction of 30% or more in blood phenylalanine concentration after 8 days of treatment with saproterin at a dose of 10mg/kg per day. The primary endpoint was mean difference between treatment groups in blood phenylalanine concentration at six weeks. Analysis was on an intention-to-treat basis. The second randomized clinical trial conducted by Trefz et al. al[2] was also a phase III, randomized, double blind, placebo controlled study screen for saproterin response among 90 children aged 4 – 12 years of age in part 1. In part 2, 46 responsive subjects were randomized (3:1) to saproterin 20mg/kg/day, or placebo for 10 weeks while continuing on a Phe-restricted diet. After 3 weeks, a dietary Phe supplement was added every 2 weeks if Phe control was adequate. Responders in part 1, were arbitrarily defined as those who achieved at least 30% reduction in blood Phe concentrations between day 1 and day 8, had blood Phe level of ≤ 300 µmol/L on day 8. The primary endpoint was daily Phe supplement tolerated by the saproterin group at week 10 compared with week 0. The Phe supplement tolerated was defined as the cumulative

increase or decrease in Phe supplement prescribed in part 2 at the last visit at which the subject had adequate blood Phe control, defined as a blood Phe concentration < 360 µmol/L.

Comparative Clinical Efficacy

Relevant Endpoints: 1) Neurocognitive and/or psychosocial functioning
2) Quality of life

Study Endpoints: 1) Mean differences between treatment groups in blood Phe level
2) The Phe supplement tolerated by the treatment group
3) Tolerability

Evidence Table

Ref./ Study Design[1]	Drug Regimens	Patient Population	N	Duration	Efficacy Results[2] (CI, p-values)	ARR / NNT[3]	Safety Results^ (CI, p-values)	ARR / NNH	Quality Rating[4]; Comments
Levy et. al.[1] Phase III, DB, PC; RCT; MC	S: Saproterin 10mg/kg/day P: placebo	Mean age (S/P): 21.5/19.5 Female (S/P): 34%/49% Blood Phe level at screening: < 600 µmol/L (S/P): 17%/19% ≥ 600 µmol/L (S/P): 83%/81% Mean (±SD) baseline blood Phe level (µmol/L): S: 843 (±300) P: 888 (± 323)	N= 88 P: 47 S: 41	6 weeks	Primary endpoint Mean differences between treatment groups in blood Phe level at week 6 (µmol): S: -245 (CI: -350 to -141; p < 0.0001) Secondary endpoints Mean differences between treatment groups in blood Phe levels at each of the 6 weeks of tx (longitudinal model with weekly blood Phe measurements: S: -230 (-317 to -144; p < 0.0001) The proportion of patients who have blood Phe level of < 600 µmol/L at week 6: S: 54% (38% to 69%; p = 0.004) P: 23% (11% to 36%)	NA NA NA	Any events (S/P): 51%/63% (p = 0.80) Serious tx related events: None recorded in either group. Discontinuation due to tx: None recorded in either group. Common Tx related events (S/P): Upper respiratory tract infection: 17%/23% Headache: 10%/13%	**NA**	**Quality Rating:** Good **Internal Validity**: **RoB** Selection: Randomization was done using a computer-generated interactive response system. Sample size is small for both groups. Low risk. Performance: Blinding of patients and study monitors. Detection: Outcome assessors were blinded. Attrition: One pt dc'd due to non-compliance. ITT analysis. **External Validity:** Recruitment: 30 sites in 8 countries across Europe and North America. Patient characteristics: Similar baseline characteristics with exception of gender for which the treatment groups differed. Outcomes: Short-term only; not true effectiveness outcomes.

Trefz el al.[2] Phase III, DB, PC, RCT; MC Part 1: screening phase (open label) Part 2: responsive subjects were randomized (DB phase)	S: Saproterin 20mg/kg/day P: placebo	Part 2: Mean age (S/P): 7.7/7. Female (S/P): 39%/50% Mean blood Phe < 300 µmol/L (S/P): 48%/42% Baseline dietary Phe intake at week 0 (mg/kg/day), mean (SD): 16.3 (8.4)*/16.8 (7.6)^ *N=30; ^N=9	N= 46* S: 33 P: 12 *One pt did not receive any study drug.	10 weeks	Part 2 Primary endpoint Daily Phe supplement tolerated a week 10 compared with week 0 (mg/kg/day) : S: 20.9 (15.4 to 26.4; p <0.001) P: 2.9 (p = NS) Secondary endpoint Difference in blood Phe level in Saproterin group between week 3 and week 0 (µmol/L) : S: -148.5 (-196 to -101; p < 0.001 P: 0 (-251 to 58; p = 0.2) The mean difference of the saproterin and placebo groups in the amount of Phe supplement tolerated at week 10 (mg/kg/day): 17.7 ± 4.5 (p < 0.001)	NA NA NA	Any events (S/P): 27%/25% (CI , p not reported) Serious tx related events: None recorded in either group. Discontinuation due to tx: None recorded in either group. Common Tx related events (S/P): Headache: 21%/8%) Rhinorrhea: 21%/0%) Cough: 15%/0%	NA	**Quality Rating:** Good **Internal Validity**: **RoB** Selection: Randomization was done using a computer-generated interactive response system. Sample size is small for all groups. Performance: Blinding of patients and study monitors. Detection: Outcome assessors were blinded. Attrition: One randomized pt did not return to clinic after 1 week washout period. ITT analysis. **External Validity** : Recruitment: Multicenter international study. Patient characteristics: Similar baseline characteristics with exception of gender for which the treatment groups differed. Outcomes: Short-term only; not true effectiveness outcomes.

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

Clinical Safety:

In 4 clinical trials, there were approximately 600 individuals with PKU took saproterin. In about 80% of cases, the length of the treatment was about 8 days. No subjects stopped treatment due to side effects in these trials. There were no serious side effects in study by Levy et.al; in part two of Trefz et al. al study, there were two serious side effects were reported (Streptococcal infection in saproterin group and appendicitis in placebo group). Overall, the adverse events from saproterin were mostly mild; the most common ones in saproterin-treated individuals included: headache, upper respiratory tract infection (common cold), and cough.

References:

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Appendix 1: Specific Drug Information[17]

CLINICAL PHARMACOLOGY

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

PHARMACOKINETICS

The absorption and elimination pharmacokinetics of mirabegron are dose-dependent.

Parameter	Result
Oral Bioavailability	Unknown
Protein Binding	Unknown
Elimination	Unknown
Half-Life	6.7 hours
Metabolism	CYP450

DOSE & AVAILABILITY

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
100mg	Tab	PO	Daily	Not defined	Not defined	> 4 years of age, same as adult dose.	Not defined	Administered with food to increase absorption, preferably at the same time every day. Saproterin tablets should be dissolved in 4-8 oz. of water of apple juice and taken within 15 minutes of dissolution.

DRUG SAFETY

Serious (REMS, Black Box Warnings, Contraindications): There are no Serious Drug Safety concerns or contradictions for saproterin at this time.

Warnings and Precautions: Treatment with saproterin should be directed by physicians knowledgeable in the management of PKU. Patients need to be monitored for blood Phe levels. Active management of dietary phe intake while taking saproterin is required to ensure adequate Phe control and nutritional balance. Drugs known to affect folate metabolism such as MTX, and their derivatives should be used with caution while taking saproterin. In addition, caution should be used when concurrent use of saproterin and levodpa and drugs affecting nitric oxide-mediated vasorelaxation (e.g., PDE-5 inhibitors such as sidenafil, vardenafil or tadalafil).

Look-alike / Sound-alike (LA/SA) Error Risk Potential:
No look-alike/sound-alike drugs have been found to have error risk potential.

Adverse Reactions
The most serious reactions during saproterin administration (regardless of relationship to treatment) were gastritis, spinal cord injury, streptococcal infection, testicular carcinoma, and urinary tract infection. The table below summarized the treatment-emergent adverse reactions that occurred in at least 4% of patients treated with saproterin in two double-blind, placebo-controlled clinical trials.

	Placebo N (%)	**Saproterin N (%)**
Number of Patients	**59**	**74**
Any Adverse Reaction	42 (71)	47 (64)
Headache	8 (14)	11 (15)
Upper Respiratory Tract Infection	14 (24)	9 (12)
Rhinorrhea	0	8 (11)
Pharyngolarygeal pain	1 (2)	7 (10)
Diarrhea	3 (5)	6 (8)
Vomiting	4 (7)	6 (8)
Cough	3 (5)	5 (7)
Pyrexia	4 (7)	5 (7)
Contusion	1 (2)	4 (5)
Abdominal Pain	5 (8)	4 (5)
Rash	4 (7)	4 (5)
Nasal congestion	0	3 (4)

Appendix 2: Abstracts of potentially relevant randomized controlled trials and/or systematic reviews

1. Efficacy of sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH4) for reduction of phenylalanine concentration in patients with phenylketonuria: a phase III randomised placebo-controlled study Harvey L Levy, MD, Andrzej Milanowski, MD′ Anupam Chakrapani, MD, Maureen Cleary, MD′ Philip Lee, MD, Friedrich K Trefz, MD, Chester B Whitley, MD, François Feillet, MD, Annette S Feigenbaum, FRCPC, Judith D Bebchuk, ScD, Heidi Christ-Schmidt, MSE, Alex Dorenbaum, MD, for the Sapropterin Research Group

Summary

Background: Early and strict dietary management of phenylketonuria is the only option to prevent mental retardation. We aimed to test the efficacy of sapropterin, a synthetic form of tetrahydrobiopterin (BH4), for reduction of blood phenylalanine concentration.

Methods: We enrolled 89 patients with phenylketonuria in a Phase III, multicentre, randomised, double-blind, placebo-controlled trial. We randomly assigned 42 patients to receive oral doses of sapropterin (10 mg/kg) and 47 patients to receive placebo, once daily for 6 weeks. The primary endpoint was mean change from baseline in concentration of phenylalanine in blood after 6 weeks. Analysis was on an intention-to-treat basis. The study is registered with ClinicalTrials.gov, number NCT00104247.

Findings: 88 of 89 enrolled patients received at least one dose of study drug, and 87 attended the week 6 visit. Mean age was 20 (SD 9·7) years. At baseline, mean concentration of phenylalanine in blood was 843 (300) µmol/L in patients assigned to receive sapropterin, and 888 (323) µmol/L in controls. After 6 weeks of treatment, patients given sapropterin had a decrease in mean blood phenylalanine of 236 (257) µmol/L, compared with a 3 (240) µmol/L increase in the placebo group (p<0·0001). After 6 weeks, 18/41 (44%) patients (95% CI 28–60) in the sapropterin group and 4/47 (9%) controls (95% CI 2–20) had a reduction in blood phenylalanine concentration of 30% or greater from baseline. Blood phenylalanine concentrations fell by about 200 µmol/L after 1 week in the sapropterin group and this reduction persisted for the remaining 5 weeks of the study (p<0·0001). 11/47 (23%) patients in the sapropterin group and 8/41 (20%) in the placebo group experienced adverse events that might have been drug-related (p=0·80). Upper respiratory tract infections were the most common disorder.

Interpretation: In some patients with phenylketonuria who are responsive to BH4, sapropterin treatment to reduce blood phenylalanine could be used as an adjunct to a restrictive low-phenylalanine diet, and might even replace the diet in some instances.

2. **Efficacy of Sapropterin Dihydrochloride in Increasing Phenylalanine Tolerance in Children with Phenylketonuria: A Phase III, Randomized, Double-Blind, Placebo-Controlled Study.** Friedrich K. Trefz, MD′ Barbara K. Burton, MD,Nicola Longo, MD, PhD, Mercedes Martinez-Pardo Casanova, MD, Daniel J. Gruskin, MD, Alex Dorenbaum, MD, Emil D. Kakkis, MD, PhD, Eric A. Crombez, MD, Dorothy K. Grange, MD, Paul Harmatz, MD, Mark H. Lipson, MD, Andrzej Milanowski, MD, PhD, Linda Marie Randolph, MD, Jerry Vockley, MD, PhD, Chester B. Whitley, MD, PhD, Jon A. Wolff, MD, Judith Bebchuk, ScD, Heidi Christ-Schmidt, MSE, Julia B. Hennermann, MD. Sapropterin Study Group

   Objective: To evaluate the ability of sapropterin dihydrochloride (pharmaceutical preparation of tetrahydrobiopterin) to increase phenylalanine (Phe) tolerance while maintaining adequate blood Phe control in 4- to 12-year-old children with phenylketonuria (PKU).

   Study design: This international, double-blind, randomized, placebo-controlled study screened for sapropterin response among 90 enrolled subjects in Part 1. In Part 2, 46 responsive subjects with PKU were randomized (3:1) to sapropterin, 20 mg/kg/d, or placebo for 10 weeks while continuing on a Phe-restricted diet. After 3 weeks, a dietary Phe supplement was added every 2 weeks if Phe control was adequate.

   Result: The mean (±SD) Phe supplement tolerated by the sapropterin group had increased significantly from the pretreatment amount (0 mg/kg/d) to 20.9 (±15.4) mg/kg/d ($P < .001$) at the last visit at which subjects had adequate blood Phe control (<360 µmol/L), up to week 10. Over the 10-week period, the placebo group tolerated only an additional 2.9 (±4.0) mg/kg/d Phe supplement; the mean difference from the sapropterin group (±SE) was 17.7 ± 4.5 mg/kg/d ($P < .001$). No severe or serious related adverse events were observed.

   Conclusions: Sapropterin is effective in increasing Phe tolerance while maintaining blood Phe control and has an acceptable safety profile in this population of children with PKU.

3. Sapropterin dihydrochloride for phenylketonuria, Usha Rani Somaraju, Marcus Merrin. *Cochrane Database of Systematic Reviews* 2012, Issue 12. Art. No.: CD008005. DOI: 10.1002/14651858.CD008005.pub3. Copyright © 2012 The Cochrane Collaboration. Published by JohnWiley & Sons, Ltd.

   A B S T R A C T

   Background: Phenylketonuria results from a deficiency of the enzyme phenylalanine hydroxylase. Dietary restriction of phenylalanine keeps blood phenylalanine concentration low. Most natural foods are excluded fromdiet and supplements are used to supply other nutrients. Recent publications report a decrease in blood phenylalanine concentration in some patients treated with sapropterin dihydrochloride. We examined the evidence for the use of sapropterin dihydrochloride to treat phenylketonuria.

   Objectives: To assess the safety and efficacy of sapropterin dihydrochloride in lowering blood phenylalanine concentration in people with phenylketonuria.

   Search methods: We identified relevant trials from the Group's Inborn Errors of Metabolism Trials Register. Date of last search: 29 June 2012. We also searched ClinicalTrials.gov and Current controlled trials. Last search: 23 July 2012. We contacted the manufacturers of the drug (BioMarin Pharmaceutical Inc.) for information regarding any unpublished trials.

   Selection criteria: Randomized controlled trials comparing sapropterin with no supplementation or placebo in people with phenylketonuria due to phenylalanine hydroxylase deficiency.

Data collection and analysis: Two authors independently assessed trials and extracted outcome data.

Main results: Two placebo-controlled trials were included.One trial administered 10mg/kg/day sapropterin in 89 children and adults with phenylketonuria whose diets were not restricted and who had previously responded to saproterin.This trial measured change in blood phenylalanine concentration. The second trial screened 90 children (4 to 12 years) with phenylketonuria whose diet was restricted, for responsiveness to sapropterin. Forty-six responders entered the placebo-controlled part of the trial and received 20 mg/kg/day sapropterin. This trial measured change in both phenylalanine concentration and protein tolerance. Both trials reported adverse events. The trials showed an overall low risk of bias; but both are Biomarin-sponsored. One trial showed a significant lowering in blood phenylalanine concentration in the sapropterin group (10 mg/kg/day), mean difference -238.80 µmol/L (95% confidence interval -343.09 to -134.51); a second trial (20 mg/kg/day sapropterin) showed a non-significant difference,mean difference -51.90 µmol/L (95%confidence interval -197.27 to 93.47). The second trial also reported a significant increase in phenylalanine tolerance, mean difference18.00 mg/kg/day (95% confidence interval 12.28 to 23.72) in the 20 mg/kg/day sapropterin group.

Authors' conclusions: There is evidence of short-term benefit from using sapropterin in some patients with sapropterin-responsive forms of phenylketonuria; blood phenylalanine concentration is lowered and protein tolerance increased. There are no serious adverse events associated with using sapropterin in the short term. There is no evidence on the long-term effects of sapropterin and no clear evidence of effectiveness in severe phenylketonuria.

Appendix 3: Suggested PA Criteria

Saproterin (Kuvan)

Goal(s):

- Promote safe and cost effective therapy for the treatment of phenylketonuria.

Length of Authorization: Initial – 2 months; Renewal – one year

Covered Alternatives: NA

Approval Criteria - Initial		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the drug prescribed by or in consultation with a specialist in metabolic disorders?	**Yes:** Go to #3	**No:** Pass to RPH; Deny (medical appropriateness)
3. Is the diagnosis tetrahydrobiopterin- (BH4-) responsive phenylketonuria?	**Yes:** Go to #4	**No:** Pass to RPh, Deny (medical appropriateness).
4. Is member currently participating in a Phe-restricted diet and unable to achieve target blood phenylalanine level?	**Yes:** Go to #5	**No:** Deny and recommend Phe-restricted diet.
5. Is member's baseline blood phenylalanine level provided in the request?	**Yes:** Approve for 2 months.	**No:** Request information from provider.
Approval Criteria – Renewal		
1) Did the patient meet the target phenylalanine level set by the specialist? AND **2)** Is the patient remaining compliant with the Phe-restricted diet?	**Yes:** Approve for 12 months.	**No:** Deny for lack of treatment response.

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