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Prior Authorization Review: sapropterin

Background:
Phenylketonuria (PKU) is the most common inherited genetic defect in amino acid metabolism. It is caused by mutations in the phenylalanine hydroxylase (PAH) gene which result in decreased phenylalanine hydroxylase activity and consequent hyperphenylalaninemia (HPA).[1] Untreated PKU can cause irreversible mental disability, behavioral abnormalities and motor impairment. Restriction of dietary phenylalanine (Phe) is the primary component of PKU management.[1] Some mutations are associated with a BH-4 phenotype and can be managed by administering exogenous tetrahydrobiopterin (BH4).[2] Approximately 2 percent of patients with elevated phenylalanine levels will have the BH4 phenotype.[2] Sapropterin (Kuvan®) is a phenylalanine hydroxylase activator indicated to reduce blood phenylalanine levels in patients with HPA due to BH4 responsive PKU.[3] It was approved by the U.S. Food and Drug Administration (FDA) in 2007 to manage BH4 responsive PKU patients along with Phe diet restrictions. The Pharmacy & Therapeutics Committee reviewed this drug previously and approved Prior Authorization (PA) for its use (see **Appendix 1**). The efficacy of sapropterin in PKU patients was established in clinical trials and confirmed in post-marketing experience. The Phenylketonuria Demographics, Outcomes, and Safety (PKUDOS) registry was established to evaluate long term safety and efficacy data on patients treated with sapropterin. To date, 504 patients have been continuously treated with sapropterin and have seen a significant decrease in blood Phe (34%, p= 0.0009) levels after 5 years of therapy.[4] Very few drug related adverse effects were reported (6%) and they included diarrhea, rhinorrhea, and headaches. Less than 1% of patients experienced serious adverse effects including cardiac arrhythmia, cholecystitis, diabetes and premature labor. No deaths have been reported for any patients maintained on sapropterin.

No other indications for sapropterin have been approved by the FDA. The efficacy of sapropterin has not been established for other types of PKU. No other off label uses of sapropterin have been evaluated. Not all patients will respond to sapropterin therapy and a 2 month therapeutic trial is necessary to assess patient response.[3] During 2015, one Prior Authorization was received and it was approved. In general, utilization of this drug is very low, which is not surprising given the small percentage of PKU patients that will benefit from exogenous tetrahydrobiopterin therapy. The American College of Medical Genetics and Genomics developed guidelines to assist in PKU diagnosis and treatment. One of the key recommendations was to recommend target blood levels of Phe in the range of 120 to 360 µmol/l for patients in all age ranges.[5]

Recommendations:
Update target Phe goals to 120 – 360 µmol/L for patients in all age ranges. No further review or research needed at this time.

References:
1. Blau N, van Spronsen FJ, Levy HL. Phenylketonuria. *The Lancet*. 2010;376(9750):1417-1427. doi:10.1016/S0140-6736(10)60961-0.

2. Shintaku H. Disorders of tetrahydrobiopterin metabolism and their treatment. *Curr Drug Metab*. 2002;3(2):123-131.

3. 'HIGHLIGHTS OF PRESCRIBING INFORMATION - KUVAN_Prescribing_Information1.pdf. http://www.kuvan.com/hcp/wp-content/file/KUVAN_Prescribing_Information1.pdf. Accessed April 6, 2016.

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4. Longo N, Arnold GL, Pridjian G, et al. Long-term safety and efficacy of sapropterin: the PKUDOS registry experience. *Mol Genet Metab*. 2015;114(4):557-563. doi:10.1016/j.ymgme.2015.02.003.

5. Vockley J, Andersson HC, Antshel KM, et al. Phenylalanine hydroxylase deficiency: diagnosis and management guideline. *Genet Med*. 2014;16(2):188-200. doi:10.1038/gim.2013.157.

Appendix 1: Current Prior Authorization Criteria.

Sapropterin (Kuvan®)

Goal(s):

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

Length of Authorization:

- Initial: 1 to 2 months; Renewal: 1 year

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 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 the patient currently compliant with a Phe-restricted diet and unable to achieve target blood phenylalanine level?	**Yes:** Go to #5	**No:** Pass to RPh. Deny and recommend Phe-restricted diet.

Approval Criteria		
5. Is the patient's baseline blood phenylalanine level provided in the request and above the target range (see Clinical Notes)?	**Yes:** Approve for 2 months if initial dose is 5-10 mg/kg/day (to allow for titration to 20 mg/kg/day). Approve for 1 month if initial dose is 20 mg/kg/day (adults and children).	**No:** Request information from provider.
Renewal Criteria		
1. Did the patient meet the target phenylalanine level set by the specialist (see Clinical Notes)?	**Yes:** Go to #2	**No:** Pass to RPh; Deny for lack of treatment response.
2. Is the patient remaining compliant with the Phe-restricted diet?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny and recommend Phe-restricted diet.

Target blood phenylalanine levels in the range of 120-360 µmol/L for patients in all age ranges.[1]
In addition to the recommended Phe concentrations, a 30% or more reduction in blood Phe is often considered a clinically significant change from baseline and should occur after the initial trial.[2] If not, the patient is a nonresponder and will not benefit from sapropterin therapy.

Doses above 20 mg/kg/day have not been studied in clinical trials.

References:
1.Vockley J, Andersson HC, Antshel KM, et al. Phenylalanine hydroxylase deficiency: diagnosis and management guideline. Genet Med. 2014;16(2):188-200. doi:10.1038/gim.2013.157
2.Blau N., Belanger-Quintana A., Demirkol M. Optimizing the use of sapropterin (BH_4) in the management of phenylketonuria. *Molecular Genetics and Metabolism* 2009;96:158-163.

P&T Review: *5/16 (DM); 11/13; 9/13; 7/13*
Implementation: *1/1/14*

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