



Therapeutic Class ReviewSM

Metabolic – Sapropterin dihydrochloride (Kuvan[®])

June 2008

New Product for Review:

Sapropterin dihydrochloride (Kuvan[®])[BioMarin]

Dossier Provided by Manufacturer: Yes

Dossier Evaluation: (3, all relevant trials included)

- 1 - Dossier missing significant clinical trial(s).
- 2 - Mfg. provided all relevant trials; Missing pharmacoeconomic model.
- 3 - Mfg. provided all relevant trials and information.

Executive Summary

Phenylketonuria (PKU) ^[1]

- PKU is a genetic disorder, resulting from a deficiency in phenylalanine hydroxylase (PAH), the enzyme required for breaking down phenylalanine (Phe) in the body.
- Phenylalanine is an amino acid obtained from food. High levels of phenylalanine can result in mental retardation, delayed speech and problems with concentration and attention.
- The annual incidence rate of PKU in the United States is one in 12,000 to 15,000 infants.

Treatment of PKU ^[1]

- Monitoring of blood phenylalanine levels ranges from once weekly to once monthly.
- Treatment is recommended when blood phenylalanine levels exceed 600 $\mu\text{mol/L}$.
- Dietary phenylalanine restriction is the standard of care, though patients often require dietary supplements in the form of medical foods containing low-phenylalanine protein sources.
- Sapropterin dihydrochloride (Kuvan) is the first medication treatment option available for patients with PKU. However, it is not effective in all patients with PKU and is not meant to replace dietary interventions.

Evidence

- All available evidence is considered uncertain or not useful for sapropterin dihydrochloride (Kuvan). Primary endpoints chosen in clinical trials were of unclear clinical significance and insufficient details were provided to evaluate trial methodology.
- Safety information is difficult to interpret because studies ranged in duration from eight days to six weeks. Randomized controlled trials of longer duration are needed to confirm that the adverse drug events observed in clinical trials can be attributed to sapropterin dihydrochloride (Kuvan).

Decision

Sapropterin dihydrochloride (Kuvan) is non-preferred/non-formulary because:

- There is no reliable evidence to support its safety and efficacy.
- Available data is limited to six weeks in duration.
- The standard of care for patients with PKU is diet restriction and there is unclear clinical benefit associated with the addition of sapropterin dihydrochloride (Kuvan).

Products

Drug Products	FDA approval ^a	Patent Expiration(s) ^b	FDA approved indications	Usual Dose/Route	Potential Off-label Uses ^c
sapropterin dihydrochloride (Kuvan [®]) ²	12/2007	12/2012	To reduce Phe levels in patients with BH4-responsive PKU	10 – 20 mg/kg/day by mouth	None listed

^a Date applies to approval date for the original brand name medication where there are now generics available.

^b Based on patents listed in Orange Book as of 04/15/2008.

^c As listed in © 1974 - 2007 Thomson MICROMEDEX database or as referenced.

References

1. Phenylketonuria: screening and management. NIH consensus statement online 2000 October 16 – 18; [cited 2008, February 28]; 17(3): 1 – 27.
2. Kuvan[®] [package insert]. Novato, CA: BioMarin Pharmaceutical Inc; December 2007.
3. Product Dossier: Kuvan[®] (sapropterin dihydrochloride), BioMarin Pharmaceutical Inc: Novato, CA. Data reviewed March 26, 2008.
4. Levy HL et al. Efficacy of sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH4) for reduction of phenylalanine concentration in patients with phenylketonuria: a phase III randomized placebo-controlled study. *Lancet* 2007; 370:504 – 10.
5. Burton BK, Grange DK, Milanowski A, et al. The response of patients with phenylketonuria and elevated serum phenylalanine to treatment with oral sapropterin dihydrochloride: a phase II, multicentre, open-label, screening study. *J Inherit Metab Dis* 2007; 30:700 – 07.
6. Poustie VJ, Wildgoose J, Rutherford P. Dietary interventions for phenylketonuria. *Cochrane Database of Systematic Reviews* 1999 Issue 3. Art. No.: CD001304.