

**Regence BlueCross BlueShield of Oregon • Regence BlueShield
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Medication Policy Manual

Policy No: dru152

Topic: Kuvan™, sapropterin dihydrochloride

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Revised/Effective Date: April 7, 2009

Next Review Date: March 2010

IMPORTANT REMINDER

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Kuvan (sapropterin dihydrochloride) is an orally administered medication used to reduce blood phenylalanine (Phe) levels in patients with phenylketonuria (PKU).

Policy/Criteria

- I.** Most contracts require prior authorization approval of sapropterin dihydrochloride prior to coverage. Sapropterin dihydrochloride may be considered medically necessary when criteria A, B and C below are met.

- A.** A diagnosis of phenylketonuria has been established by a metabolic specialist.

AND

- B.** Phenylalanine levels cannot be maintained within the recommended maintenance range with dietary intervention alone (see Appendix I).

AND

- C.** Documentation of an average baseline blood phenylalanine level is provided prior to initiating therapy with sapropterin dihydrochloride.

- II.** Administration, Quantity Limitations, and Authorization Period

- A.** Regence considers sapropterin dihydrochloride to be a self-administered medication.

- B.** When prior authorization is approved, sapropterin dihydrochloride may be authorized in doses of 20 mg/kg/day. Doses exceeding 20 mg/kg/day are considered investigational.

- C.** Authorization Period

- 1.** Initial authorization: Authorization shall be reviewed at 2 months to confirm that blood phenylalanine level has decreased at least 30% from baseline (the phenylalanine value provided in criterion I.C. above).

- 2.** Continued authorization: After the initial authorization, authorization shall be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

- III.** Sapropterin dihydrochloride is considered not medically necessary when used for any condition other than phenylketonuria.

Position Summary

- Sapropterin dihydrochloride is approved for the reduction of blood Phe levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin (BH4) responsive PKU. Sapropterin dihydrochloride should be used in conjunction with a Phe-restricted diet.
- Sapropterin dihydrochloride is a synthetic form of BH4, a cofactor required for metabolism of Phe to tyrosine. Without this cofactor, excess Phe accumulates in the blood and tissues.
- Untreated PKU is associated with severe mental retardation, reduced IQ scores, behavioral difficulties and other symptoms.
- The standard treatment for patients with PKU is maintaining a diet with a low Phe content. Sapropterin dihydrochloride is the first medication indicated for the treatment of PKU.
- In clinical trials, patients were considered responders to sapropterin dihydrochloride if blood Phe levels decreased at least 30% from baseline. A response was seen as early as eight days after initiating treatment. ^[2, 3, 5, 6]
- Clinical trials ranged in duration from eight days to six weeks. Only one of four trials was a published, randomized, double-blind, placebo controlled study. ^[2, 3]
- Sapropterin dihydrochloride is available through limited distribution.

Clinical Efficacy

- The recommended starting dose of sapropterin dihydrochloride is 10 mg/kg/day taken once daily. For patients who do not respond, the dose can be increased to 20 mg/kg/day. The efficacy and safety of higher doses has not been established.
- In a phase-I, open-label, uncontrolled screening study of 489 patients with PKU, 20% of patients achieved at least a 30% decrease in blood Phe levels with sapropterin dihydrochloride treatment. ^[2, 6]
 - * Sapropterin dihydrochloride was dosed at 10 mg/kg/day and patients were not on Phe restricted diets.
 - * The study duration was eight days which may be insufficient time to demonstrate an adequate response.

- After a washout period, 88 of the above mentioned patients who responded to sapropterin dihydrochloride were randomized to six weeks of treatment with either sapropterin dihydrochloride or placebo. [3]
- * All patients had either relaxed or abandoned a strict low-Phe diet at the time of screening.
- * The primary efficacy endpoint was the change in blood Phe concentration from baseline to week six. Of the patients treated with sapropterin dihydrochloride, 44% demonstrated at least a 30% reduction in Phe concentration, compared with 9% of patients treated with placebo.
- * Eighty patients who completed the randomized, controlled trial were enrolled in a 22-week, open-label, extension trial. The patients that still enrolled at the end of study had an average decrease of -190.5 (SD 355.7) micromoles/L from week 0 to week 22. [5]
- The long-term impact of sapropterin dihydrochloride on neurological development is unknown. There is no evidence to indicate that sapropterin dihydrochloride improves long-term patient outcomes.

Safety

- Available evidence of safety and efficacy in controlled trials is limited to treatment of up to 10 weeks duration. [1]
 - The most common side effects observed in clinical trials include headache, upper respiratory infection, rhinorrhea, pharyngolaryngeal pain, diarrhea, nausea and vomiting^[1].
- The most serious adverse reactions during sapropterin dihydrochloride administration (regardless of relationship to treatment) were gastritis, spinal cord injury, streptococcal infection, testicular carcinoma, and urinary tract infection. [1]
- - The safety and efficacy of sapropterin dihydrochloride in children under the age of four has not been established in clinical trials. [1]

Appendix 1: Recommended Maintenance Phe Levels for Classical PKU as per The National Institutes of Health (NIH) Consensus Statement ^[4]

Age Range	Maintenance Phe Levels
Neonates through 12 years of age	120 – 360 µmol/dL (2 – 6 mg/dL)
Greater than 12 years of age	120 – 900 µmol/dL (2 – 15 mg/dL)
During pregnancy	120 – 360 µmol/L (2 – 6 mg/dL)

References

1. Kuvan [package insert]. Novato, CA: BioMarin Pharmaceutical Inc.; December 2007.
2. Product Dossier: KuvanTM (sapropterin dihydrochloride). BioMarin Pharmaceutical Inc.; Novato, CA. Reviewed January 30, 2008.
3. 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.
4. Phenylketonuria: screening and management. NIH consensus statement online 2000 October 16 – 18; [cited 2008, February 28]; 17(3): 1 – 27.
5. Lee P, Treacy EP, Crombez E, et. al. ; Sapropterin Research Group. Safety and efficacy of 22 weeks of treatment with sapropterin dihydrochloride in patients with phenylketonuria. *Am J Med Genet A*. 2008 Nov 15;146A(22):2851-9.
6. 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 Oct;30(5):700-7.

Cross References
None

Codes	Number	Description
N/A		