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Index: Benefits

TO: ALL COUNTY CALIFORNIA CHILDREN SERVICES (CCS) PROGRAM
AND GENETICALLY HANDICAPPED PERSONS PROGRAM (GHPP)
ADMINISTRATORS, MEDICAL CONSULTANTS, STATEWIDE
CONSULTANTS AND STATE SYSTEMS OF CARE DIVISION STAFF

SUBJECT: AUTHORIZATION OF SAPROPTERIN DIHYDROCHLORIDE (KUVAN™)

I. PURPOSE

The purpose of this Numbered Letter (N.L.) is to disseminate policy for the California Children's Services (CCS) Program and the Genetically Handicapped Persons Program (GHPP) regarding the revised criteria and process for the authorization of sapropterin dihydrochloride.

This letter supersedes N.L. 01-0109 Sapropterin Dihydrochloride (Kuvan™) as a CCS Benefit.

II. BACKGROUND

Phenylketonuria (PKU) is a genetic disorder characterized by a deficiency or absence of the hepatic enzyme phenylalanine hydroxylase (PAH). PAH is required for the conversion of the essential amino acid phenylalanine (PHE) to tyrosine. When PAH is not present or present in insufficient quantities abnormally high PHE levels accumulate in the blood and brain leading to a variety of complications including abnormal brain development, impaired cognitive ability, mental illness, tremors, and seizures. In adolescents and adults, high levels of PHE may lead to psychiatric symptoms, which may interfere with work, school, and diminish quality of life.

PKU requires lifelong treatment to reduce and prevent adverse consequences associated with the excessive accumulation of PHE. The cornerstone of PKU treatment is a PHE restricted diet, which severely limits the intake of protein from meat, fish, dairy, and grain products. Many individuals with PKU require nutritional replacement products such as metabolic formulas and specially formulated low-protein foods to obtain adequate nutrition for appropriate growth and cognitive development. Dietary restriction of PHE throughout life is required for optimal neurological and developmental outcomes. However, long-term use of the restrictive diet has been associated with complications of low bone mass such as osteopenia, osteoporosis, and fractures.¹ Also, for individuals with PKU, especially those not consuming specially formulated low-protein foods, there is an increased risk of inadequate nutrient intake of copper, manganese, zinc, iron, B₆, B₁₂, and essential fatty acids.²

Due to the limiting nature of the diet or inadequate access to low-protein therapeutic foods, many individuals find adherence to the PHE restrictive diet difficult to maintain. This is especially true for adolescents and young adults. Asthma, recurrent headaches, eczema, neurological symptoms, hyperactivity and/or lethargy, phobias, and depression have all been reported by adults who discontinue dietary treatment.^{3, 4}

Currently, the only United States Food and Drug Administration (FDA) approved pharmacologic product for the treatment of PKU, in conjunction with a PHE restricted diet, is KuvanTM (sapropterin dihydrochloride). KuvanTM is a synthetic form of 6R-BH₄ (tetrahydrobiopterin), a naturally occurring enzyme cofactor. In individuals with tetrahydrobiopterin (BH₄) responsive PKU, sapropterin dihydrochloride works in conjunction with PAH to increase PAH activity and lower serum PHE levels.

¹ MacLeod, E.L. & Ney, D.M. Nutritional management of phenylketonuria. *Ann Nestle Eng.* 2010; 68: 58-69.

² Singh, R.H., Rohr, F., Frazier, D., et al. Recommendations for the nutrition management of phenylalanine hydroxylase deficiency. *Genetics in Medicine.* 2014; 16(2), 121- 130.

³ Koch, R., Burton, B., Hoganson, G., et al. Phenylketonuria in adulthood: a collaborative study. *J Inherit Metab Dis.* 2012; 25, 333-346.

⁴ Brumm, V.L., Bilder, D., Waisbren, S.E. Psychiatric symptoms and disorders phenylketonuria. *Mol Genet Metab.* 2010; 99 (supp 11): S59-S63.4

Approximately 25% to 50% of patients with PAH deficiency are sapropterin-responsive. “Patients with mild PAH deficiency are most likely to respond because some stable protein is required for sapropterin to function; nonetheless, responsive patients are identified among those with complete PAH deficiency.”⁵ Since prediction of sapropterin responsiveness by genotype-phenotype correlation is not exact, the American College of Medical Genetics and Genomics (ACMG) recommends, “that every PAH-deficient patient should be offered a trial of sapropterin therapy to assess responsiveness except those with two null mutations in *trans*.”⁵

The ACMG identifies responsiveness to sapropterin dihydrochloride as a clinically significant decline in blood PHE levels, an increase in PHE tolerance, or an improvement in neuropsychiatric symptoms such as depression, anxiety, or attention disorders. For patients with late-treated PAH deficiency, either on a restricted or unrestricted PHE diet, improvements in behavior, psychiatric symptomology or seizure control constitutes responsiveness.⁵

The ACMG currently recommends that blood phenylalanine levels be maintained in the 120 – 360 micromoles/liter range for all individuals. Liberalization of blood phenylalanine levels in adults is no longer advised as elevated levels of phenylalanine may lead to psychological issues such as depression, anxiety, and phobias. “Any combination of therapies that facilitate improvement in blood PHE levels for a given individual is appropriate; therapies may be combined and should be individualized.”⁵ For the 25% to 50% of individuals who are sapropterin hydrochloride responsive, KuvanTM or a similar drug may play a pivotal role in the management of their PAH deficiency disorder.

III. POLICY

- A. Effective the date of this N.L., sapropterin dihydrochloride is a benefit for CCS Program clients \geq 1 month of age and GHPP clients with a diagnosis of PKU, whose care is authorized by a CCS Program/GHPP approved metabolic Special Care Center (SCC).
- B. Sapropterin dihydrochloride may be considered as an adjunctive therapy, to be used with a phenylalanine restricted diet, for any PAH deficient CCS Program/GHPP eligible client.

⁵ Vockley, J., Andersson, H.C., Antshel, K.M., et. al. Phenylalanine hydroxylase deficiency: diagnosis and management guidelines. *Genetics in Medicine*. 2014: 16(2), 188 – 200.

- C. A therapeutic trial period that documents responsiveness to the use of sapropterin dihydrochloride must be completed prior to the authorization for ongoing treatment.
- D. Sapropterin dihydrochloride is available for authorization as a tablet for oral use or a powder for oral solution.
- E. Blood PHE levels should be obtained per ACMG guidelines. However, the SCC Program/CCS metabolic physician may order PHE levels as indicated.
- F. Authorization of sapropterin dihydrochloride for genetic disorders other than PKU, such as tetrahydrobiopterin (BH₄) deficiency disorders, requires approval from a Statewide Medical Consultant and will be reviewed on a case-by-case basis.

IV. POLICY IMPLEMENTATION

- A. Sapropterin dihydrochloride is an “excluded” drug and requires a separate authorization.
 - 1. For CCS Program clients, all requests for sapropterin dihydrochloride as a treatment for PKU will be reviewed and approved by the CCS County Medical Consultant or a System of Care Division (SCD) Medical Consultant prior to authorization. All requests for use as a treatment for BH₄ deficiencies will be reviewed and acted upon by a Statewide Medical Consultant.
 - 2. For GHPP clients, all requests for sapropterin dihydrochloride will be reviewed and acted upon by the designated GHPP staff.
- B. Therapeutic Trial
 - 1. A trial, not to exceed two months, of sapropterin dihydrochloride to determine responsiveness, may be authorized upon submission of the following documentation:
 - a. For CCS Program clients, a CCS-paneled metabolic physician’s written plan of treatment, including plans for monitoring PHE levels during the trial period.

- b. For GHPP clients, a metabolic SCC physician's written plan of treatment, including plans for monitoring PHE levels during the trial period.
 - c. For CCS Program and GHPP clients, a CCS Program/SCC paneled registered dietitian's (RD) medical nutrition therapy plan (MNT) including evaluation of ongoing compliance with a phenylalanine-restricted diet.
 - d. For CCS Program and GHPP clients, results of one or more baseline blood PHE levels obtained within three months prior to the request and two blood PHE levels obtained during the trial period.
2. The trial should be completed within three months of the authorization.
 3. At least one of the following criteria must be met to determine responsiveness and justify continued therapy with the medication:

- a. A clinically significant reduction in blood PHE:

Clinical judgment is required to determine what constitutes a clinically significant decline in blood PHE. A 30% reduction is frequently regarded as responsive. However, for individuals with a PHE level at the lower end of the treatment range (180 micromoles/liter or lower), a significant or 30% decline is rarely seen even if they are sapropterin-responsive.

- b. An increase in PHE tolerance:

For individuals with a PHE level at the lower end of the treatment range, responsiveness is evaluated by gradually increasing dietary PHE to determine if there is an increase in PHE tolerance without an increase in blood PHE levels. Increase in tolerance is determined by maintenance of low blood PHE levels or improvement in neuropsychiatric symptoms with increased dietary PHE. In some individuals, the increase in tolerance may be two to three times above baseline.

- c. A documented improvement in neuropsychiatric symptoms, improved seizure control or enhanced mental functioning leading to improved functioning at school, work or social obligations.

C. Continued Authorization

1. Continued authorization of sapropterin dihydrochloride requires the following be submitted:
 - a. Request from a SCC metabolic authorized physician which includes pertinent medical reports with justification for continued use.
 - (1) Following the therapeutic trial, justification should include at least one baseline PHE level and two additional PHE levels obtained during the trial and the criteria used for determining responsiveness.
 - (2) For subsequent reauthorizations, justification should include at least one blood PHE level obtained within the last three months of use of the medication and documented rationale for continuation.
 - b. An annual request for prescription renewal from a SCC metabolic authorized physician.
 - c. A CCS Program/SCC registered dietitian's (RD) medical nutrition therapy plan including appropriate growth charts and evaluation of ongoing compliance with a phenylalanine-restricted diet dated within the last six months of the request. CCS Program and GHPP clients are to be assessed at least every six months by the CCS Program/SCC RD. For GHPP adult men and non-pregnant women with well-controlled and stable blood PHE levels within the recommended range of 120 – 360 micromoles/liter, one RD assessment per year may be done via telecommunication.
 - d. Annual SCC team assessment per CCS Program requirements or more often if indicated with physician, dietitian and social worker reports.
2. For CCS Program clients, all requests for continued use of sapropterin hydrochloride will be reviewed and approved by the CCS County Medical Consultant or the SCD Medical Consultant prior to authorization.
3. For GHPP clients, all requests for continued use of sapropterin dihydrochloride will be reviewed and acted upon by the designated GHPP staff member.

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The SCD will continue to monitor changes with the pharmacotherapy for PKU as additional drugs are currently at various stages of the clinical trials process, and will update this policy as warranted. If you have any questions regarding this N. L., please contact your CCS County Medical Consultant or Dr. Marcia Ehinger at (916) 327-3012 or via e-mail at Marcia.ehinger@dhcs.ca.gov.

Sincerely,

ORIGINAL SIGNED BY ROBERT J. DIMAND

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