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Director

State of California—Health and Human Services Agency
Department of Health Care Services



ARNOLD SCHWARZENEGGER
Governor

DATE: March 19, 2009

N.L.: 01-0109
Index: Benefits

TO: ALL COUNTY CALIFORNIA CHILDREN SERVICES (CCS) PROGRAM
ADMINISTRATORS, MEDICAL CONSULTANTS, AND STATE
CHILDREN'S MEDICAL SERVICES (CMS) AND GENETICALLY
HANDICAPPED PERSONS PROGRAM (GHPP) BRANCH STAFF

SUBJECT: SAPROPTERIN DIHYDROCHLORIDE (KUVANT™)

I. PURPOSE

The purpose of this numbered letter is to establish CCS and GHPP policy regarding the authorization of sapropterin dihydrochloride as an adjunctive treatment for phenylketonuria management.

II. BACKGROUND

Phenylketonuria (PKU) is a genetic disorder characterized by a deficiency or absence of the enzyme phenylalanine hydroxylase (PAH). Phenylalanine (Phe) is an essential amino acid. PAH is required for the conversion of Phe to tyrosine. If the active enzyme PAH is not present in sufficient quantities, Phe accumulates to abnormally high levels in the blood and brain, resulting in a variety of complications including impaired cognitive ability, mental illness, tremors and seizures. The spectrum of disease with impaired phenylalanine metabolism ranges from benign hyperphenylalaninemia to classic PKU with absence or severe deficiency of PAH. Poorly controlled PKU leads to abnormal brain development, impaired cognitive ability, seizures, tremors and behavioral disorders including ADHD in children. In adolescents and adults, high Phe levels may lead to psychiatric symptoms and impairment in attention and information processing speed.

PKU requires lifelong treatment and is very effectively managed by a Phe-restricted diet, which uses nutritional replacement products such as metabolic formulas and specially-manufactured low protein foods. Ongoing adherence to a strict Phe restricted diet with resulting lower Phe levels may, however, be difficult for some patients.

Currently the only United States Food and Drug Administration approved pharmacologic product for treatment of PKU, in conjunction with a phenylalanine restricted diet, is

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sapropterin dihydrochloride (Kuvan™). Kuvan™ is a synthetic form of 6R-BH4 (tetrahydrobiopterin), a naturally occurring enzyme cofactor. In individuals with tetrahydrobiopterin (BH4) responsive PKU, Kuvan™ works in conjunction with PAH to increase the PAH activity and lower serum Phe levels. In an uncontrolled clinical trial done by the manufacturer, 20 percent of patients responded to Kuvan™, with response defined as a lowering of the Phe level by 30 percent from the pre-treatment level. Because only a small percentage of individuals respond to Kuvan™, and because there is no marker or laboratory test that predicts responsiveness to Kuvan™, a therapeutic trial of Kuvan™ with measurement of serum phenylalanine level before and after the trial period, must be done for each potential recipient.

III. POLICY

Effective the date of this letter sapropterin dihydrochloride (Kuvan™) is a benefit of the CCS and GHPP programs for clients over four years of age with PKU, whose care is authorized to a CCS/GHPP approved metabolic Special Care Center (SCC) and who meet the medical criteria as outlined in this N.L. Kuvan™ may be considered as an adjunctive therapy, to be used with a phenylalanine-restricted diet, for certain forms of PKU, particularly when the Phe level is in the 600-1200 micromol/liter (µmol/L) range. a therapeutic trial period that documents response to the use of Kuvan™ must be completed prior to authorization of ongoing treatment.

IV. POLICY IMPLEMENTATION

- A. Sapropterin dihydrochloride (Kuvan™) is an "excluded" drug and requires a separate authorization.

All requests for Kuvan shall be reviewed by the CCS County Medical Consultant or CCS Regional Office Medical Consultant who will determine the *medical necessity* for the authorization

- B. Therapeutic Trial

A trial of sapropterin dihydrochloride of no more than two months duration may be authorized upon submission of an evaluation by the authorized metabolic SCC team, completed within the three months prior to the request, indicating client's ongoing care is managed by the SCC team, and which includes:

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- Physician's written plan of treatment, indicating the expectation that by the end of the two month trial the Phe level shall be reduced by at least 30 percent from pretreatment levels.
- Nutritionist report with an evaluation of the ongoing compliance with a Phe restricted diet with use of metabolic enteral product and/or medical foods and a detailed treatment plan that describes no modification of Phe intake during the trial period.
- Comprehensive social worker report with an evaluation of the child and family's understanding and reaction to medical condition and ability to follow the prescribed medical regimen.
- Results of one or more baseline blood Phe levels obtained within three months prior to the request and two additional blood Phe levels obtained within the year prior to initiation of treatment.

C. Ongoing Authorization

1. Authorization of sapropterin dihydrochloride beyond the trial period requires documentation of the following: copies of laboratory reports showing a reduction in the client's Phe levels that are equal to or greater than 30 percent from baseline established prior to the trial period, and consistent with the goal established in the physician's treatment plan.
2. Ongoing authorization requires not only that the CCS or GHPP client maintain program eligibility, but that there also be:
 - Submission of a report from the physician at the Metabolic SCC at least every three months, including reports of Phe levels performed at least monthly, for the first 12 months of treatment.
 - Submission of a report from the physician at the Metabolic SCC at least every six months after the first 12 months of treatment, that must document Phe levels remaining within the desired range and obtained at least every three months.
 - Submission of a full SCC team assessment at least annually as per CCS program requirements or more often if indicated, with physician, nutritionist and social work reports.

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D. CCS program staff shall consult with the CCS Regional Office Medical Consultant when requests for authorization of sapropterin dihydrochloride are made in the following situations.

- Requests for clients whose Phe levels during the trial period closely approach but do not reach a 30 percent reduction
- Requests for authorization of clients under four years old.
- Requests for authorization of clients who are already receiving sapropterin dihydrochloride at the time of initial CCS request, such as from participation in a clinical trial or where provided by another funding source.

If you have any questions regarding this N. L., please contact your CCS Regional Office Medical Consultant.

Sincerely,

Original Signed by Harvey Fry for Luis R. Rico

Luis R. Rico, Acting Chief
Children's Medical Services Branch