CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205065Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	205-065
Priority or Standard	Standard
Submit Date(s)	2/8/2013
Received Date(s)	2/8/2013
PDUFA Goal Date	12/6/2013
Division / Office	DGIEP/ODE III
Reviewer Name(s)	Lara Dimick-Santos, MD, FACS
Review Completion Date	November 5, 2013
Established Name	Sapropterin hydrochloride
(Proposed) Trade Name	Kuvan (powder)
Therapeutic Class	Phenylalanine Hydroxylase (b) (4) Activator
Applicant	BioMarin
Formulation(s)	Powder – 100mg packets
Dosing Regimen	5, 10, or 20 mg/kg/day
Indication(s)	Reduction of blood Phe levels in patients with hyperphenylalaninemia due to BH4-responsive phenylketonuria (PKU)
Intended Population(s)	Patients with BH4-responsive PKU

Clinical Team Leader Summary

Kuvan® is indicated to reduce blood phenylananine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydropbiopterin- (BH4) responsive Phenylketonuria (PKU). Kuvan is used in conjunction with a Phe-restricted diet. BioMarin has developed a new powder formulation for the same indication to be packaged in a unit dose packet for administration as an oral solution. Kuvan powder formulation is designed to improve the taste, flavor and appearance of sapropterin dihydrochloride, and is expected to offer a convenient alternative to tablets. It offers the benefit of short reconstitution time and solution clarity upon powder dissolution.

There is no new clinical information submitted with this NDA for a new dosage form of Kuvan. The Clinical Pharmacology and Biopharmaceutics reviewers have reviewed the submitted data and recommend approval of this new powder dosage form. However, the CMC review concludes that the NDA is not approvable at this time as the "Acceptable" site recommendation from the Office of Compliance is pending, and the Labels/Labeling has not been finalized. There are no other outstanding CMC issues.

I agree with the conclusions of the other reviewers, noted below, that this NDA is approvable pending the site inspection recommendation is "Acceptable" and the labeling is finalized and acceptable to the Agency. The box and container labels have been approved at the time of this review.

Regulatory History

The proposed unit dose packet of Kuvan powder formulation and the currently marketed Kuvan tablet both deliver an identical dose of the active pharmaceutical ingredient, sapropterin dihydrochloride. A Type C meeting was held on June 21, 2012, to discuss whether Kuvan powder for oral solution qualifies for a Biowaiver. Based on the data/information provided by BioMarin, the FDA agreed that biowaiver may be granted.

As a follow-up to the Type C meeting FDA communicated to BioMarin that a new NDA is required since the Kuvan powder formulation is a new dosage form.

The drug was granted Orphan Drug Status on January 29, 2004.

Nonclinical Pharmacology

There is no new nonclinical data submitted with this NDA the labeling was reviewed by Yuk-Chow Ng, PhD, who agrees with approval. There has not been an Established Pharmacologic Class EPC previously assigned to this product and the proposal "phenylalanine hydroxylase (b) (4) activator" is acceptable to Dr. Ng. Dr. Ng also made several recommendations for changes to the applicants proposals for labeling in the following Sections:

8.1 Pregnancy
8.3 Nursing Mothers
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Please see his complete review for the specific recommendations

CMC

CMC review is performed by Caroline Strasinger, PhD in the Office of New Drug Quality Assessment, Division II, Branch IV.
Her review is summarized below.

Kuvan powder for oral solution dosage form was developed to facilitate administration of the drug product with various liquids. It offers the benefit of short reconstitution time and solution clarity upon powder dissolution.

The quality of the drug product is controlled by tests for identity, appearance, (b) (4) (b) (4), content uniformity, dissolution, assay, related substances and microbial purity.

The Applicant is requesting 18 months of expiration dating; it is granted based on registration and supportive stability data provided during the review cycle indicating the product is stable through 9 months.

The drug substance used to manufacture the drug product is the same drug substance as that used to manufacture commercial KUVAN® tablets (NDA 22181). According to NDA 22181, the drug substance has a retest date of (b) (4) months and has been shown to be stable up to (b) (4) months.

However, the CMC review concludes that the NDA is not approvable at this time as the "Acceptable" site recommendation from the Office of Compliance is pending, and the Labels/Labeling has not been finalized. There are no other outstanding CMC issues.

Clinical Pharmacology

The clinical pharmacology review was performed by Insook Kim, PhD.
The sponsor is requesting a biowaiver for the Kuvan powder for oral solution on the basis that each dose unit (tablet or packet) delivers an identical quantity of sapropterin (b) (4) the primary excipient (mannitol) between Kuvan tablets and the Kuvan powder. Invivo BA and/or BE can be waived for oral solutions on the assumption that release of the drug substance is self-evident provided "that the solutions do not contain any excipient that significantly affects drug absorption" per 21 CFR 320.22(b)(3)(i).

The new powder formulation contains sucralose which is not present in Kuvan tablets. Each packet of 100 mg Kuvan powder contains (b) (4) of sucrolase. The sponsor provided literature in order to support their view that "there is no

consensus in the scientific literature about the potential influence of sucralose on the absorption and bioavailability of drugs."

In her review, Dr Kim states that there is no adequate information to draw a conclusion of the significant effects of sucralose on the activity of CYP3A4, CYP2D6 and p-gp in humans. Nevertheless considering the available information, the incorporation of sucralose in the Kuvan powder formulation should not preclude a biowaiver for this product based on followings:

- At the highest recommended dose of 20 mg/kg/day, the intake of sucralose per Kuvan dosing given once a day is (b) (4). While the study has limitations to draw a conclusion, no effects of (b) (4) on intestinal P-gp, CYP3A4, or CYP2D1 (rat equivalent to human CYP2D6) protein expression were observed at 100 mg/kg/day, the dose equivalent to (b) (4) sucralose.

- It seems unlikely that CYP3A4 and CYP2D6 have significant roles in metabolism of sapropterin based on the currently available information.

- Although it is unknown if p-gp has any significant role in absorption of Kuvan, the potential for clinically significant under dosing seems low because blood phenylalanine level would be regularly monitored as a part of clinical management of PKU even in the case of hypothetical inductive effect of sucralose on p-glycoprotein protein expression.

- Sucralose as an alternative sweetener is compatible with phenylketonuria. Since the approval of Kuvan Tablets, Kuvan is recommended to be taken with food which may also contain sucralose.

Biopharmaceutics

Biopharmaceutics review was performed by Kelly M. Kitchens, Ph.D. Her review is summarized below.

The Applicant's bases for a biowaiver request are summarized below:

1. The powder formulation delivers an identical quantity of active pharmaceutical ingredient (b) (4) the primary excipient, mannitol, as the tablet formulation.
2. Sapropterin dihydrochloride is very soluble in aqueous solutions (greater than 1 g/mL) and exhibits rapid dissolution.
3. The excipient sucralose, which is present in the powder formulation but not in the tablet formulation, does not affect drug absorption and bioavailability.
4. The osmolarity of Kuvan Powder is similar to that of Kuvan Tablets in water and in apple juice.

RECOMMENDATION:

Based on the information submitted for the composition, solubility, and osmolarity of Kuvan (sapropterin dihydrochloride) Powder for Oral Solution, the waiver for in-vivo bioavailability/bioequivalence studies is granted. From the Biopharmaceutics perspective, NDA 205,065 for Kuvan (sapropterin dihydrochloride) Powder for Oral Solution is recommended for approval.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LARA DIMICK-SANTOS
11/05/2013