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APPLICATION NUMBER:

205065Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	November 18, 2013
From	Marie Kowblansky, Ph.D., CMC Lead CDER/ONDQA/Division II
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 205065
Applicant	BioMarin Pharmaceutical Inc.
Date of Submission	February 8, 2013
PDUFA Goal Date	December 8, 2013
Proprietary Name / Established (USAN) names	KUVAN Sapropterin dihydrochloride
Dosage forms / Strength	Powder for Oral Solution single dose packets: 100mg sapropterin dihydrochloride (equivalent to 76.8 mg sapropterin base)
Proposed Indication(s)	reduction of blood phenylalanine levels in patients with hyperphenylalaninemia (HPA)
Recommended:	Approval [pending: 1) a recommendation from the Office of Compliance that all sites involved in the manufacture and testing of this product are "Acceptable" and 2) finalization of all labeling]

1. Introduction

Kuvan® (sapropterin dihydrochloride) Powder for Oral Solution is indicated for reduction of blood phenylalanine levels in patients with hyperphenylalaninemia. The product will be packaged in single dose packets containing 100mg of sapropterin dihydrochloride (equivalent to 76.8 mg sapropterin base). Biomarin currently markets KUVAN® as a tablet formulation, with administration instructions calling for dissolving the tablet in 4 to 8 oz. (120-240 mL) of water or apple juice. The approved tablet formulation and the proposed Powder for Solution, both deliver the same dose of the active ingredient. This new powder formulation is designed to yield a solution with improved taste and appearance over that of the dissolved tablet solution. This is being filed as a 505(b)(1) application with some cross referencing to the approved Kuvan Tablet NDA (22-181). The majority of the submitted information relates to the chemistry and controls used in the manufacture of this product.

There is no IND associated with this application and no clinical data have been submitted; for approval of this product; the sponsor is relying on previous findings of efficacy and safety for Kuvan® Tablets and has requested a biowaiver for conducting *in vivo* BA/BE studies.

Since the proposed product is a new dosage form for a currently approved drug substance, this is classified as a Type 3 application.

2. CMC

Kuvan® Powder for Oral Solution is prepared in unit-dose, multi-layered, (b) (4) laminate packets, each containing 100 mg of sapropterin dihydrochloride equivalent to 76.8 mg

sapropterin base. As mentioned above, KUVAN® was previously approved under NDA 22181 (December 2007) as a 100 mg sapropterin dihydrochloride tablet formulation. The powder and the tablet formulations contain an identical quantity of sapropterin dihydrochloride, but otherwise differ in composition. Both formulations contain sapropterin dihydrochloride drug substance in combination with mannitol, and ascorbic acid. However, the powder also contains sucralose (b) (4) and potassium citrate (b) (4), with no other formulation components, while the tablet contains crospovidone (b) (4), calcium phosphate (b) (4), sodium stearyl fumarate (b) (4).

The drug substance used in this product is the same as used in the manufacture of commercial Kuvan Tablets under NDA 22181: same manufacturer, same process, and same specifications. Consequently, the applicant references NDA 22181 (KUVAN Tablets) for all drug substance information.

The product specification will include testing for appearance, loss on drying, ascorbic acid content, content uniformity, dissolution, assay, related substances, and microbial purity. All tests and acceptance criteria were judged by the CMC reviewer to be appropriate and sufficient for this type of product, assuring its identity, strength, quality and purity. Based on the 9-month stability data that were submitted, an 18-month expiration dating period is recommended.

While there are no unresolved CMC review issues, Dr. Caroline Strasinger, the CMC reviewer, has concluded that this application cannot be approved from the CMC perspective until 1) a recommendation is received from the Office of Compliance that all sites involved in the manufacture and testing of this product are "Acceptable" and 2) all labeling is finalized.

3. Nonclinical Pharmacology/Toxicology

Dr. Yuk-Chow NG, the nonclinical pharmacology/toxicology reviewer, has concluded that from a nonclinical pharmacology standpoint, the NDA is approvable. No new nonclinical toxicology studies were conducted in connection with this NDA; the safety of sapropterin dihydrochloride has been established from the toxicology studies conducted under NDA 22-181. There are no safety concerns for this new formulation of sapropterin dihydrochloride.

The reviewer also finds acceptable the sponsor's proposal to use "phenylalanine hydroxylase enzyme activator" for designating the Established Pharmacologic Class (EPC) for this product.

Dr. Ng has also recommended some labeling changes to the following sections of the package insert: 8.1 Pregnancy, 8.3 Nursing Mothers, and 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

4. Clinical Pharmacology/

Drs. Jeremiah Momper and Insook Kim, the Clinical Pharmacology reviewers, have judged this application to be acceptable from a Clinical Pharmacology standpoint. Their review focused on the potential effect of sucralose on drug absorption in the current formulation, since it is absent from the tablet formulation. An understanding of this effect was critical to determining whether the sponsor's biowaiver request could be granted based on 21 CFR 320.22 (b)(3)(i): *in-vivo* BA and/or BE studies can be waived for solutions that "do not contain any excipient that significantly affects drug absorption". Based on literature, they concluded that "Overall, considering the available evidence, the incorporation of sucralose in the Kuvan powder formulation should not prohibit a Biowaiver for this product", but they deferred to the ONDQA Biopharmaceutics reviewer for a final decision whether a biowaiver should be granted.

Dr. Kelly Kitchens, the Biopharmaceutics reviewer has concluded that based on the composition of the current product, high solubility of the drug substance, and solutions of similar osmolarity when the powder or tablet formulations are dissolved, a biowaiver for *in-vivo* BA/BE is granted and approval of this NDA is recommended.

5. Clinical Microbiology

Not Applicable

6. Clinical

The indication, target population, route of administration, and strength of the proposed powder formulation are the same as for the approved KUVAN Tablets. Because the two formulations were judged bioequivalent by the Clinical Pharmacology and Biopharmaceutics no clinical studies were required for this application. Dr Lara Dimick, the clinical reviewer, agrees with the recommendation of the Clinical Pharmacology and Biopharmaceutics reviewers, recommending that this application be approved from the clinical perspective.

7. Advisory Committee Meeting --

Not Applicable

8. Pediatrics.

Kuvan was granted Orphan Drug Designation on January 29, 2004 (Orphan Designation #03-1815), and in accordance with Section 505B(g) of Food, Drug and Cosmetic Act and Title 21 CFR 314.55(d) is exempt from the requirement of providing data to assess the safety and effectiveness for a new dosage form in all relevant pediatric populations.

9. Other Relevant Regulatory Issues

- Kuvan® (sapropterin dihydrochloride) Tablets was approved in December 2007
- The drug was granted Orphan Drug Status in January, 2004

10. Labeling

Only minor revisions to the label have been recommended by Lisa V. Khosla, reviewer for the Division of Medication Errors Prevention Analysis (DMEPA). Our recommendations have been transmitted to BioMarin.

11. Recommendations/Risk Benefit Assessment

BioMarin has marketed KUVAN® tablets in the US since December, 2007. Administration instructions call for dissolution of the tablet in water or apple juice prior to administration. The currently proposed powder product, which also requires dissolution in water or apple juice prior to administration, is designed as an alternative to the tablet product to improve the taste of the administered solution

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There are no unresolved issues or deficiencies that need to be conveyed to the sponsor. No PMRs, PMCs, or pediatric studies need to be requested.

Based on recommendations from all disciplines involved in the review of this application, this NDA should be approved, pending 1) an “Acceptable” recommendation for the sites involved in the manufacture of this product and 2) completion of labeling negotiations with the sponsor. (No major labeling issues have been identified at the present time.)

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/s/

MARIE KOWBLANSKY
11/19/2013