CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205065Orig1s000

PHARMACOLOGY REVIEW(S)

ADDENDUM TO PHARMACOLOGY/TOXICOLOGY REVIEW OF NDA 205,065 DATED October 28, 2013

Reviewer: Yuk-Chow Ng, Ph.D.

Date: 11/07/2013

In the Sponsor's proposed labeling, the EPC (Established Pharmacologic Class) text phrase, "phenylalanine hydroxylase (b) (4) activator" was proposed for Kuvan (sapropterin dihydrochloride). After a review of the literature, this reviewer, as well as the medical team, concurred with the Sponsor's proposed EPC text phrase. Dr. Paul Brown, ODE Associate Director for Pharmacology/ Toxicology in the OND Immediate Office, was consulted since a new EPC text phrase will be created for Kuvan. (b) (4) The review team concurred with this recommendation. Therefore, the EPC text phrase for Kuvan will be "phenylalanine hydroxylase activator"

Yuk-Chow Ng, Ph.D. Date
Pharmacologist
Division of Gastroenterology and Inborn Errors Products

David B. Joseph, Ph.D. Date
Pharmacology Team Leader
Division of Gastroenterology and Inborn Errors Products

cc:
NDA 205,065
DGIEP
DGIEP/PM
DGIEP/D. Joseph
DGIEP/Y.-C. Ng
OND IO/P. Brown

R/D Init.: D. Joseph 11/26/13

APPENDIX/ATTACHMENTS
None

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

/s/

YUK-CHOW NG
12/02/2013

DAVID B JOSEPH
12/02/2013
I concur.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	205,065
Supporting document/s:	001
Applicant's letter date:	02/08/2013
CDER stamp date:	02/08/2013
Product:	Kuvan® (sapropterin dihydrochloride) Powder for Oral Solution
Indication:	To reduce blood phenylalanine levels in patients with hyperphenylalaninemia due to tetrahydrobiopterin- (BH4-) responsive phenylketonuria
Applicant:	BioMarin Pharmaceutical Inc. Novato, CA
Review Division:	Gastroenterology and Inborn Errors Products
Reviewer:	Yuk-Chow Ng, Ph.D.
Supervisor/Team Leader:	David B. Joseph, Ph.D.
Division Director:	Donna Griebel, M.D.
Project Manager:	Jessica Benjamin

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 205,065 are owned by BioMarin Pharmaceutical Inc. or are data for which BioMarin Pharmaceutical has obtained a written right of reference. Any information or data necessary for approval of NDA 205,065 that BioMarin Pharmaceutical does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 205,065.

TABLE OF CONTENTS

Reference ID: 3396934

1 Executive Summary

1.1 Introduction

Kuvan is a synthetic form of tetrahydrobiopterin (BH4), the cofactor for the enzyme phenylalanine hydroxylase (PAH). PAH hydroxylates phenylalanine (Phe) through an oxidative reaction to form tyrosine. In patients with Phenylketonuria (PKU), PAH activity is absent or deficient. Treatment with BH4 activates residual PAH enzyme, improves the normal oxidative metabolism of Phe, and decreases Phe levels in some patients. Kuvan® Tablets was approved in 2007, and is indicated to reduce blood Phe levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4-) responsive PKU. Kuvan® is to be used in conjunction with a Phe-restricted diet.

The current submission is for a powder for oral solution formulation of Kuvan®. The Sponsor did not submit any new nonclinical studies to support the current application. All nonclinical toxicology studies were submitted and reviewed previously under NDA 22-181. The tablets and powder for oral solution differ in their excipients. There are no safety concerns regarding the excipients in the newly proposed formulation.

1.2 Brief Discussion of Nonclinical Findings

No new nonclinical studies were submitted.

1.3 Recommendations

1.3.1 Approvability

The application is recommended for approval.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

Established Pharmacologic Class

Kuvan® Tablets was approved in 2007 under NDA 22-181, and is indicated for the treatment of hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4-) responsive phenylketonuria (PKU). An Established Pharmacologic Class has not been assigned to this product. The Sponsor proposes “phenylalanine hydroxylase (b) (4) activator” as the Established Pharmacologic Class (EPC) text phrase for sapropterin dihydrochloride. This proposal is evaluated below.

The active ingredient in Kuvan® is sapropterin dihydrochloride, which is a synthetic form of tetrahydrobiopterin (BH4). It has been well established that BH4 is an essential co-

factor for PAH (phenylalanine hydroxylase), and is critical in the conversion of phenylalanine (Phe) to tyrosine (Heintz et. al., Human Mutation 2013, 34, 927). In patients with hyperphenylalaninemia due to BH4-responsive phenylketonuria, treatment with Kuvan activates residual PAH enzyme activity, improves the normal oxidative metabolism of Phe, and decreases blood Phe levels in these patients. Thus, Kuvan is considered a cofactor and activator of the enzyme PAH. The proposed EPC text phrase is appropriate as it is based on the mechanism of action of sapropterin, and therefore is scientifically valid. In addition, the medical team concurs that the proposed classification is clinically meaningful.

Sponsor's Proposed Version:

5 (b) (4) (b) (4) When Co-administering Kuvan and Drugs Known to Affect Nitric Oxide-Mediated Vasorelaxation

(b) (4)
drugs that affect nitric oxide-mediated vasorelaxation (e.g., PDE-5 inhibitors such as sildenafil, vardenafil, or tadalafil), because both sapropterin dihydrochloride and PDE-5 inhibitors may induce vasorelaxation. The additive effect of sapropterin and PDE-5 inhibitor co-administration could lead to a reduction in blood pressure; however, the combined use of these medications has not been evaluated in humans. In animal studies, orally administered Kuvan in combination with a PDE-5 inhibitor had no effect on blood pressure.

Evaluation:

The section is identical to that of the current label and no modification is needed.

Sponsor's Proposed Version:

8.1 Pregnancy

Pregnancy Category C

(b) (4)

(b) (4)

Recommended Version:

8.1 Pregnancy

Pregnancy Category C. A patient registry has been established that also collects data on women who are treated with Kuvan during pregnancy. For more information regarding the registry program call 1-866-906-6100.

Risk Summary
There are no adequate and well-controlled studies with Kuvan in pregnant women. An embryo-fetal development study with sapropterin dihydrochloride in rats using oral doses up to 3 times the maximum recommended human dose (MRHD) given during the period of organogenesis showed no effects. In a rabbit study using oral administration of sapropterin dihydrochloride during the period of organogenesis, a rare defect, holoprosencephaly, was noted at 10 times the MRHD. A moderate increase in the incidence of early resorbed fetuses also was noted in the dams at the same oral dose. Kuvan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations
Disease-associated maternal and/or embryofetal risk
Available data from the Maternal Phenylketonuria Collaborative Study on 468 pregnancies and 331 live births in PKU-affected women demonstrated that uncontrolled Phe levels above 600 µmol/L are associated with a very high incidence of neurological, cardiac, facial dysmorphism, and growth anomalies. Good dietary control of Phe levels

during pregnancy is essential to reduce the incidence of Phe-induced teratogenic effects.

Animal Data
No effects on embryo-fetal development were observed in a reproduction study in rats using oral doses of up to 400 mg/kg/day sapropterin dihydrochloride (about 3 times the MRHD of 20 mg/kg/day, based on body surface area), administered during the period of organogenesis. However, in a rabbit reproduction study, oral administration of a maximum dose of 600 mg/kg/day (about 10 times the MRHD, based on body surface area) during the period of organogenesis was associated with an increase (not statistically significant) in the incidence of holoprosencephaly, compared to controls.

Sponsor's Proposed Version:

8.3 Nursing Mothers

Evaluation:

The section has been modified in collaboration with the Maternal Health Team (Drs. Carrie Ceresa and Jeanine Best).

Recommended Version:

It is not known whether Kuvan is present in human milk. Sapropterin is present in the milk of intravenously, but not orally treated lactating rats. The developmental and health benefits of human milk feeding should be considered along with the mother's clinical need for Kuvan and any potential adverse effects on the human milk-fed child from the drug or from the underlying maternal condition. Exercise caution when Kuvan is administered to a nursing woman.

Sponsor's Proposed Version:

12.1 Mechanism of Action

Kuvan is a synthetic form of BH4, the cofactor for the enzyme phenylalanine hydroxylase (PAH). PAH hydroxylates Phe through an oxidative reaction to form tyrosine. In patients with PKU, PAH activity is absent or deficient. Treatment with BH4

can activate residual PAH enzyme, improve the normal oxidative metabolism of Phe, and decrease Phe levels in some patients.

Evaluation:

This section is identical to that of the current label and no modification is needed.

Sponsor's Proposed Version:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 2-year carcinogenicity study was conducted in F-344 rats, and a 78-week carcinogenicity study was conducted in CD-1 mice. In the 104-week oral carcinogenicity study in rats, sapropterin doses of 25, 80, and 250 mg/kg/day (0.2, 0.7, and 2 times the maximum recommended human dose of 20 mg/kg/day, respectively, based on body surface area) were used. In the 78-week oral carcinogenicity study in mice, sapropterin doses of 25, 80, and 250 mg/kg/day (0.1, 0.3, and 2 times the recommended human dose, respectively, based on body surface area) were used. In the 2-year rat carcinogenicity study, there was a statistically significant increase in the incidence of benign adrenal pheochromocytoma in male rats treated with the 250 mg/kg/day (about 2 times the maximum recommended human dose, based on body surface area) dose, as compared to vehicle-treated rats. The mouse carcinogenicity study showed no evidence of a carcinogenic effect, but the study was not ideal due to its duration of 78 instead of 104 weeks.

Sapropterin was genotoxic in the *in vitro* Ames test at concentrations of 625 µg (TA98) and 5000 µg (TA100) per plate, without metabolic activation. However, no genotoxicity was observed in the *in vitro* Ames test with metabolic activation. Sapropterin was genotoxic in the *in vitro* chromosomal aberration assay in Chinese hamster lung cells at concentrations of 0.25 and 0.5 mM. Sapropterin was not mutagenic in the *in vivo* micronucleus assay in mice at doses up to 2000 mg/kg/day (about 8 times the maximum recommended human dose of 20 mg/kg/day, based on body surface area). Sapropterin, at oral doses up to 400 mg/kg/day (about 3 times the maximum recommended human dose, based on body surface area) was found to have no effect on fertility and reproductive function of male and female rats.

Evaluation:

The chemical term "dihydrochloride" should be added after "sapropterin" to reflect the complete chemical structure of the test article used in the studies described in this section.

Recommended Version:

A 2-year carcinogenicity study was conducted in F-344 rats, and a 78-week carcinogenicity study was conducted in CD-1 mice. In the 104-week oral carcinogenicity study in rats, sapropterin dihydrochloride doses of 25, 80, and 250 mg/kg/day (0.2, 0.7, and 2 times the maximum recommended human dose of 20 mg/kg/day, respectively, based on body surface area) were used. In the 78-week oral carcinogenicity study in mice, sapropterin dihydrochloride doses of 25, 80, and 250 mg/kg/day (0.1, 0.3, and 2 times the recommended human dose, respectively, based on body surface area) were used. In the 2-year rat carcinogenicity study, there was a statistically significant increase in the incidence of benign adrenal pheochromocytoma in male rats treated with the 250 mg/kg/day (about 2 times the maximum recommended human dose, based on body surface area) dose, as compared to vehicle-treated rats. The mouse carcinogenicity study showed no evidence of a carcinogenic effect, but the study was not ideal due to its duration of 78 instead of 104 weeks.

Sapropterin dihydrochloride was genotoxic in the *in vitro* Ames test at concentrations of 625 µg (TA98) and 5000 µg (TA100) per plate, without metabolic activation. However, no genotoxicity was observed in the *in vitro* Ames test with metabolic activation. Sapropterin dihydrochloride was genotoxic in the *in vitro* chromosomal aberration assay in Chinese hamster lung cells at concentrations of 0.25 and 0.5 mM. Sapropterin dihydrochloride was not mutagenic in the *in vivo* micronucleus assay in mice at doses up to 2000 mg/kg/day (about 8 times the maximum recommended human dose of 20 mg/kg/day, based on body surface area). Sapropterin dihydrochloride, at oral doses up to 400 mg/kg/day (about 3 times the maximum recommended human dose, based on body surface area) was found to have no effect on fertility and reproductive function of male and female rats.

2 Drug Information

2.1 Drug

Generic Name

sapropterin dihydrochloride

Code Name

SUN 0588

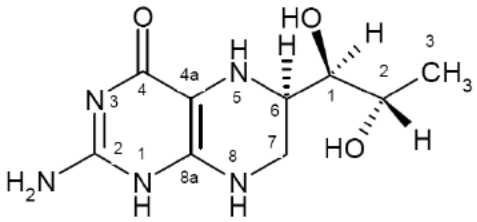
Chemical Name

(6R)-2-amino-6[(1R,2S)-1,2-dihydroxypropyl]-5,6,7,8-tetrahydro-4(1H)-pteridinone dihydrochloride

Reference ID: 3396934

Molecular Formula/Molecular Weight

$C_9H_{15}N_5O_3 \cdot 2HCl$ / 314.17



• 2 HCl

Pharmacologic Class: phenylalanine hydroxylase enzyme activator

2.2 Relevant INDs, NDAs, and DMFs

IND 103,435 (Sapropterin dihydrochloride, BioMarin Pharmaceutical Inc.)
NDA 22-181 (Kuvan®, BioMarin Pharmaceutical Inc.)

2.3 Drug Formulation

The Kuvan powder formulation for oral solution is a white to yellow powder. Each packet contains 100 mg of the active ingredient sapropterin dihydrochloride, equal to 76.8 mg sapropterin. The components and quantitative composition of each packet are shown in the following table (taken from the Sponsor's submission).

Components	Pharmacopoeial Standard	Function	Quantity (mg/packet)
Sapropterin dihydrochloride	NA	Active ingredient	100.0
Mannitol	USP/ Ph. Eur.	(b) (4)	(b) (4)
Potassium Citrate	USP/ Ph. Eur.		
Sucralose, NF	NF		
Ascorbic acid	USP/Ph. Eur.		
		Total	

2.4 Comments on Novel Excipients

Mannitol, potassium citrate, and ascorbic acid are listed in the U.S. FDA Food Additive Status List as GRAS/FS (substances generally recognized as safe in foods but limited in standardized foods where the standard provides for its use) according to 21 CFR 184.1091.

In addition, mannitol is present at comparable levels in the approved tablet formulation of Kuvan ((b) (4)), and the maximum daily intake is

(b) (4). Therefore, the maximum daily intake of mannitol from Kuvan powder is not considered to be a safety concern.

Regarding potassium citrate, JECFA (Joint FAO/WHO Expert Committee on Food Additives) evaluated the acceptable daily intake (ADI) of citric acid and its calcium, potassium, and sodium salts. JECFA concluded that citric acid and its salts do not constitute a significant toxicological hazard to man, and set no ADI limit for their consumption. The Food and Nutrition Board of the Institute of Medicine recommends 4700 mg as an adequate daily intake of potassium, and JECFA sets no ADI limit for potassium chloride. At the maximum proposed dose of 20 mg/kg/day sapropterin dihydrochloride, the maximum daily intake of potassium citrate, based on a 60-kg bodyweight, will be (b) (4). Therefore, the maximum daily intake of potassium citrate from Kuvan powder is not considered to be a safety concern.

Regarding ascorbic acid, the Food and Nutrition Board Recommended Daily Allowance (RDA) is 75 to 90 mg, and the upper limit is 2000 mg. At the maximum proposed dose of 20 mg/kg/day sapropterin dihydrochloride, the maximum daily intake of ascorbic acid, based on a 60-kg bodyweight, will be (b) (4). Therefore, the maximum daily intake of ascorbic acid from Kuvan powder is not considered to be a safety concern.

Regarding sucralose, the FDA-recommended ADI is 5 mg/kg/day (Federal Register, Vol. 63, No. 64, pg. 16417-16433, 1998). At the maximum proposed dose of 20 mg/kg/day sapropterin dihydrochloride, the total daily intake of sucralose will be (b) (4) (b) (4) which is lower than the ADI. Therefore, the maximum daily intake of sucralose from Kuvan powder is not considered to be a safety concern.

2.5 Comments on Impurities/Degradants of Concern

N/A

2.6 Proposed Clinical Population and Dosing Regimen

Kuvan is indicated to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4-) responsive phenylketonuria (PKU). Kuvan is to be used in conjunction with a Phe-restricted diet. The recommended starting dose of Kuvan is 10 mg/kg taken once daily. Dose levels may be adjusted in the range of 5 to 20 mg/kg once daily. Kuvan powder for oral solution is to be dissolved in 4 to 8 oz. (120-240 mL) of liquid and consumed within 30 minutes of preparation.

2.7 Regulatory Background

Kuvan® Tablets was approved in 2007 under NDA 22-181, and is indicated for the treatment of hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4-) responsive phenylketonuria (PKU). It is to be used in conjunction with a Phe-restricted

diet. The current submission is for the approval of a powder for oral solution formulation of Kuvan.

3 Studies Submitted

No new studies were submitted.

4 Pharmacology

No new studies were submitted.

5 Pharmacokinetics/ADME/Toxicokinetics

No new studies were submitted.

6 General Toxicology

No new studies were submitted.

7 Genetic Toxicology

No new studies were submitted.

8 Carcinogenicity

No new studies were submitted.

9 Reproductive and Developmental Toxicology

No new studies were submitted.

10 Special Toxicology Studies

No new studies were submitted.

11 Integrated Summary and Safety Evaluation

Kuvan (sapropterin dihydrochloride) is a synthetic form of tetrahydrobiopterin (BH4), the endogenous cofactor for the enzyme phenylalanine hydroxylase (PAH). PAH hydroxylates Phe (phenylalanine) through an oxidative reaction to form tyrosine. In patients with PKU, PAH activity is absent or deficient. Treatment with BH4 activates residual PAH enzyme, improves the normal oxidative metabolism of Phe, and decreases Phe levels in some patients. Kuvan Tablets was approved in 2007, and is indicated for the treatment of hyperphenylalaninemia (HPA) due to tetrahydrobiopterin-(BH4-) responsive phenylketonuria (PKU). It is to be used in conjunction with a

Phe-restricted diet. The current submission is for a powder for oral solution formulation of Kuvan.

In the current NDA, the Sponsor did not submit any new nonclinical studies. All nonclinical toxicology studies were submitted and reviewed previously under NDA 22-181 by Dr. Fang Cai. The following is a brief summary of the toxicology studies taken from Dr. Cai's review, dated 11/27/2007.

"Acute (single-dose) toxicity studies of sapropterin via p.o., i.v. and s.c. administrations were performed in mice, rats and marmosets. The minimal lethal doses (MLDs) for mice were 256 mg/kg for males and 320 mg/kg for females (i.v.). The MLDs for both male and female mice were 204 mg/kg (s.c) and 1000 mg/kg (p.o.). The MLDs for both male and female rats were 320 mg/kg (i.v.). The MLDs were 1250 mg/kg for male rats and 2500 mg/kg for female rats (p.o.). The MLDs were 1125 mg/kg for male rats and 1687.5 mg/kg for female rats (s.c.). The MLD for monkeys was not determined after i.v. administration and was 2000 mg/kg for p.o. administration. The MLD was 300 mg/kg for male monkey and was not determine for female monkey (s.c.). The MLD for 7-day old male and female rats was 1200 mg/kg. The MLDs were 1717 mg/kg for juvenile male mice (p.o) and 2330 mg/kg for juvenile female mice (p.o.). After p.o. administration to juvenile rats, the MLDs were 2330 mg/kg for males and 3162 mg/kg for females. Transient tremor, ataxia, tachypnea, and decreased motor activity were observed in adult rats and mice after i.v administration. In marmoset monkeys, salivation, emesis, yellow staining around the mouth and genitalia were noted. In addition, the female monkeys were subdued with marked tremor, ataxia and sluggish movements before death. Hunched posture, decreased motor activity, respiratory difficulties, ataxia and piloerection were seen in juvenile mice and rats after p.o.

Repeat dose oral toxicity studies were conducted in adult rats and marmosets. Hypertrophy of parafollicular cells of the thyroid was noted in both rat and monkey toxicity studies. Increased incidence of pituitary gland hyperplasia occurred at doses ≥ 40 mg/kg/d in 52-week rat study. In the 13-Week monkey study, enteritis was observed in 320 mg/kg/d females. Toxicity of the kidney (dilated distal tubules, dilated Bowman's capsule, thickened glomerular membrane), liver (centriacinal lymphoid follicle, mineralized fibrous focus) and the ovary (regressing corpora lutea, luteinizing artretic follicles) was observed at doses of 80 and 320 mg/kg/d. In a 52-Week monkey study, increased incidences in cerebellar basophilic concretions in the brain, chronic ileitis and myocardial fibrosis were observed with no dose-related increase in incidence or severity. Increased incidences in transitional cell hyperplasia (kidney, male of 80 mg/kg/d) and lymphoid hyperplasia (stomach, 320 mg/kg/d group) were observed. Glandular hyperplasia and adenomyosis (uterus) was observed in females dosed 20 and 320 mg/kg/d. In repeated oral dose toxicity study in juvenile rats (2 and 4-week), basophilia of proximal tubules, dilatation of renal tubules and pelvis, and thickened Bowman's capsule occurred at 320 mg/kg/d.

Sapropterin tested positive in the bacterial reverse mutation and chromosome aberration tests but was not mutagenic when assessed in the *in vivo* mouse micronucleus test.

The carcinogenic potential of sapropterin was assessed in a 104-week oral carcinogenicity study in rats and a 78-week oral carcinogenicity study in mice. There was a dose-related increase in incidence of benign adrenal pheochromocytoma in male rats. The incidence of benign adrenal pheochromocytoma in high dose (250 mg/kg/day) male rats was significantly increased relative to the control group. In female mice, a slight but non-significant increase in incidence of pulmonary adenoma was observed at the mid dose (80 mg/kg/day) and high dose (250 mg/kg/day). However, the mouse study was not ideal due to its duration of only 78 weeks.

In the fertility and early embryonic development study in rats, sapropterin at a oral dose up to 400 mg/kg/d did not produce any effects on fertility and reproductive functions of male and female rats. Teratogenicity studies with sapropterin have been conducted in rats at oral doses up to 400 mg/kg/day and in rabbits at oral doses up to 600 mg/kg/day. Sapropterin was not teratogenic in rats. However, there was a significant reduction in the number of live fetuses and a significant reduction in the body weights of live fetuses from F1 dams treated with the 400 mg/kg/day dose. In the rabbit teratogenicity study, there was a significant increase in the incidence of holoprosencephaly at the 600 mg/kg/day compared to controls. In the post-natal and peri-natal developmental rat study with sapropterin, the average number of still births was increased in 40 and 400 mg/kg/d dams and birth rate was also decreased in 400 mg/kg/d dams. An increased incidence of newborn pups (F2) with thymic cervical residue was noted in all treated groups.

Sapropterin HCl had no antigenic potential under the conditions of the studies in guinea pigs and mice."

In summary, the proposed formulation (powder for oral solution) of Kuvan appears to be safe, based on the available safety information for the excipients. Furthermore, there are no safety concerns related to the proposed dose levels of sapropterin dihydrochloride or the intended patient population, since these are the same as for Kuvan Tablets.

cc:
ORIG NDA 205,065
DGIEP
DGIEP/PM
DGIEP/D. JOSEPH
DGIEP/Y.C. NG
DGIEP/L. DIMICK-SANTOS
R/D INIT.: D. JOSEPH 10/24/13

12 Appendix/Attachments

None

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

/s/

YUK-CHOW NG
10/27/2013
The application is recommended for approval.

DAVID B JOSEPH
10/28/2013
I concur.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 205,065 **Applicant: Biomarin** **Stamp Date: 02/08/2013**

Drug Name: Kuvan (sapropterin dihydrochloride) **NDA Type: 505 (b)(1)**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			N/A No new studies were submitted.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			N/A
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			N/A
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			N/A
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N/A
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?			N/A
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			N/A
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			N/A
11	Has the applicant addressed any abuse potential issues in the submission?		X	
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Yuk-Chow Ng, Ph.D. 3/19/2013

Reviewing Pharmacologist Date

David Joseph, Ph.D. 3/19/2013

Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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/s/

YUK-CHOW NG
03/25/2013
fileable

DAVID B JOSEPH
03/28/2013