

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205065Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

<i>NDA</i>	205-065	<i>Submission Date(s)</i>	February 9, 2013
<i>Brand Name</i>	Kuvan		
<i>Generic Name</i>	Sapropterin dihydrochloride		
<i>Reviewer</i>	Jeremiah Momper, Pharm.D., Ph.D. Insook Kim, Ph.D.		
<i>Team Leader</i>	Sue-Chih Lee, Ph.D.		
<i>OCP Division</i>	Division of Clinical Pharmacology 3		
<i>OND Division</i>	Division of Gastroenterology and Inborn Errors Products		
<i>Sponsor</i>	Biomarin Pharmaceutical Inc.		
<i>Submission Type</i>	Original		
<i>Formulation; Strengths; Regimen</i>	Powder for Oral Solution 10 mg/kg/day taken once daily with food and may be adjusted in the range of 5 to 20 mg/kg taken once daily		
<i>Indication</i>	Reduction of phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4) responsive Phenylketonuria (PKU)		

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1 Executive Summary

Submitted is a new formulation of Kuvan (sapropterin dihydrochloride). Kuvan was approved in 2007 for the reduction of phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4) responsive Phenylketonuria (PKU). Kuvan is available as tablets at 100 mg strength. It is recommended to dissolve Kuvan tablets in 120-240 ml of water or apple juice before administration and the dissolved solution should be taken within 15 minutes based on the administration method studied in phase 3 trials for the approval of Kuvan tablets. (b) (4)

In this submission, the sponsor proposes a new powder formulation for oral solution. The proposed new powder formulation is to be dissolved in 120-240 ml of liquid and consumed

within 30 minutes of preparation. Kuvan powder for oral solution will be available as a unit dose packet containing 100 mg of sapropterin dihydrochloride. There were no new clinical studies conducted with the proposed powder formulation and the sponsor proposes to rely on the safety and efficacy of the approved Kuvan tablets.

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. In-vivo 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 sucralose. 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.” This review is focused on the potential role of sucralose on the oral absorption of sapropterin. There are no clinical pharmacology specific labeling updates for new formulation.

1.1 Recommendations

The Office of Clinical Pharmacology reviewed the submission and found acceptable from a clinical pharmacology standpoint. Final decision of granting a biowaiver grant is deferred to biopharmaceutics reviewers at the Office of New Drug Quality Assessment.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

In our review, 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 underdosing 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.

The active ingredient of Kuvan, sapropterin is a synthetic version of endogenous co-factor tetrahydrobiopterin (BH4) and the metabolic pathway of sapropterin is assumed to be same as for BH4. The metabolism and recycling of BH4 is mediated by the enzymes dihydrofolate reductase and dihydropteridine reductase¹ (Figure 1). It is unknown if transporters such as p-gp play a role in sapropterin absorption.

Kuvan tablet is recommended to be taken with food. Sucralose is compatible with phenylketonuria and is present in many dietary products as an alternative sweetener. Each packet of 100 mg Kuvan powder contains (b)(4) of sucralose. The amount of sucralose intake from Kuvan powder will vary depending on the dose for an individual patient. At the highest dose of Kuvan, 20 mg/kg the intake of sucralose per dosing will be (b)(4) for 10 kg-and 80 kg patients, respectively. This amount is equivalent to (b)(4) of sucralose for Kuvan powder given once a day. To put this in a context, a standard (b)(4) of sucralose.

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Figure 1. Metabolism of tetrahydrobiopterin (BH4); From Ann. Rev. Nurr. 1988. 8:185-209

The sponsor provided literatures for the potential effects of sucralose on oral absorption via modulation of p-glycoprotein and cytochrome p-450 enzymes (please see attached memorandum by Dr. Jeremiah Momper for more details). One study to date provides evidence that sucralose

¹ Nenad Blau, Inborn errors of pterin metabolism, Ann. Rev. Nurr. 1988. 8:185-209

may have an effect on drug absorption and bioavailability via induction of P-glycoprotein and cytochrome p450 enzymes. In this study, the authors noted that the dose-dependent increase in protein expression of P-gp, CYP3A4, and CYP2D1 (the *rat* equivalent of the human enzyme CYP2D6) after 12 week-treatment of Splenda® (1.1% sucralose) at doses higher than 100 mg/kg/day Splenda®. On the other hand, no effects of Splenda® on intestinal P-gp, CYP3A4, or CYP2D1 protein expression were observed at 100 mg/kg/day, the dose equivalent to 1.1 mg/kg/day sucralose².

This study provided preliminary evidence that sucralose may alter transporter and/or metabolic enzyme expression in the gastrointestinal tract and thus affect bioavailability of drug substrates. However, this study done in rats using Splenda® product has several important limitations, including failure to assess transporter and enzyme activity. Additionally, other components of the marketed Splenda product, such as maltodextrin, were not adequately controlled for to conclude the contribution of sucralose on the observed dose-dependent increase in P-gp, CYP3A4, or CYP2D1 protein expression. No data is available to evaluate the potential effects of sucralose on p-glycoprotein and P450 enzyme in humans.

² Abou-Donia MB, El-Masry EM, Abdel-Rahman AA, McLendon RE, Schiffman SS. Splenda alters gut microflora and increases intestinal p-glycoprotein and cytochrome p-450 in male rats. *J Toxicol Environ Health A*. 2008;71(21):1415-29.

4 Appendices

4.1 Memorandum

MEMORANDUM TO FILE

Date: April 4, 2013

From: Jeremiah Momper, Pharm.D., Ph.D.
Commissioner's Fellow, Office of Clinical Pharmacology

To: Insook Kim, Ph.D., Clinical Pharmacology Reviewer
Office of Clinical Pharmacology, DCP3

Sue Chih Lee, Ph.D., Team Leader
Office of Clinical Pharmacology, DCP3

NDA: 205065

Sponsor: Biomarin Pharmaceutical Inc

Drug: Kuvan (Sapropterin) powder formulation

Background

BioMarin currently markets an approved Kuvan Tablet (100 mg sapropterin dihydrochloride) under NDA 22181 (approval date December 13, 2007). Kuvan is indicated to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4-) responsive phenylketonuria (PKU). Kuvan tablets are intended be dissolved in 120 to 240 mL of water or apple juice prior to oral administration. There is extensive variability in C_{max} and AUC across the different modes of administration and meal conditions. Metabolic enzymes and drug transporters involved in sapropterin disposition have not been characterized.

BioMarin has developed a new powder formulation for administration as an oral solution to be packaged in a unit dose packet. The drug product components and quantitative composition per packet are shown in Table 1. Sucralose and potassium citrate are excipients in the Kuvan packet that are not present in the tablet formulation.

Table 1. Drug Product Components and Quantitative Composition Per Packet

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			

BioMarin is requesting a biowaiver for the the Kuvan powder for oral solution on the basis that each dose unit (tablet or packet) delivers an identical quantity of sapropterin dihydrochloride and (b) (4) the primary excipient (mannitol). Per the FDA Guidance, "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations (March 2003)" and 21 CFR 320.22(b)(3)(i) entitled: "Bioavailability and Bioequivalence (April 2011)", in-vivo 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".

During a Type C meeting held on June 21, 2012 to discuss the biowaiver, FDA noted that sucralose has been reported to potentially affect absorption and bioavailability of drugs. Biomarin 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."

Review of Sponsor's Provided Literature Sources

The sponsor provided the following two literature sources:

Abou-Donia MB, El-Masry EM, Abdel-Rahman AA, McLendon RE, Schiffman SS. Splenda alters gut microflora and increases intestinal p-glycoprotein and cytochrome p-450 in male rats. *J Toxicol Environ Health A*. 2008;71(21):1415-29.

Brusick D, Borzelleca JF, Gallo M, Williams G, Kille J, Wallace Hayes A, Xavier Pi-Sunyer F, Williams C, Burks W. Expert panel report on a study of Splenda in male rats. *Regul Toxicol Pharmacol*. 2009 Oct;55(1):6-12

The publication by Aboi-Donia et al. describes a study in which Splenda (comprised of the high-potency artificial sweetener sucralose and the fillers maltodextrin and glucose) was administered

by oral gavage at 100, 300, 500, or 1000 mg/kg/d to male Sprague-Dawley rats for 12 weeks. Fecal samples were collected weekly for bacterial analysis and measurement of fecal pH. After 12 weeks, half of the animals from each treatment group were sacrificed to determine the intestinal expression of the membrane efflux transporter P-glycoprotein (P-gp) and the cytochrome P-450 (CYP) enzymes CYP3A4 and CYP2D1 by Western blot. The remaining animals were allowed to recover for an additional 12 weeks, at which point further assessments of fecal microflora, fecal pH, and expression of P-gp and CYP were determined. While the authors report that Splenda is associated with a reduction in beneficial fecal microflora and an increase in body weight relative to control, this critique will focus on the effect of Splenda on the intestinal expression of P-glycoprotein and CYP450 metabolic enzymes.

Relative to the control, the 12 week treatment with 100 mg/kg Splenda exerted no apparent effect on the expression of P-gp, whereas the expression of P-gp with 300 mg/kg Splenda increased markedly by 143.5% and with 500 mg/kg by 122.6%, while the expression of P-gp at 1000 mg/kg decreased significantly by 64% at the end of the 12 week treatment. At the end of the 12 week recovery from 100 mg/kg Splenda, there was no effect on P-gp expression, whereas P-gp was significantly elevated after recovery from 300 mg/kg Splenda by 16%, from 500 mg/kg by 56.8%, and from 1000 mg/kg by 82.2% relative to the control.

Relative to control, the 12 week treatment with 100 mg/kg Splenda exerted no apparent effect on the expression of CYP3A4 and CYP2D1. The expression of CYP3A4 at 300 mg/kg increased markedly by 43.5%, at 500 mg/kg by 70%, and at 1000 mg/kg by 151.3% relative to control. The expression of CYP2D1 at 300 mg/kg increased markedly by 36.7%, at 500 mg/kg by 152.1%, and at 1000 mg/kg by 249.3%. After recovery, the expression of CYP3A4 was significantly increased by 22.4% only at 1000 mg/kg, and the expression of CYP2D1 at 500 mg/kg was significantly increased by 32.9% and at 1000 mg/kg by 22.1% relative to control.

The authors conclude that “the present finding of increased expression of P-gp and CYP proteins by Splenda at the low dosages used in this experiment is clinically important with regard to potential drug interactions.” However, there are several issues which require consideration:

- 1) While the increase in the expression of CYP3A4 and CYP2D1 was linear and dose dependent, the expression of P-gp was nonlinear. This finding is unexpected since the nuclear receptor PXR (pregnane X receptor) is involved in xenobiotic induction of both CYP3A4 and P-gp. CYP3A4 is co-localized with P-gp in enterocytes, and there is extensive overlap in coinducibility of CYP3A4 and P-gp.
- 2) Attributing the effects observed in this study to sucralose alone is premature given that the Splenda product tested is comprised predominantly of maltodextrin. No experimental group was included to control for any potential effects of maltodextrin. Although maltodextrin would be expected to be hydrolyzed to glucose in the duodenum and thus potentially have no role in altering P-gp/CYP450 enzyme expression, this still should be controlled for experimentally before the results can be broadly extrapolated.
- 3) Sucralose had no effect on the protein expression of P-gp, CYP3A4, and CYP2D1 at doses of [REDACTED]^{(b)(4)} dosage of 100 mg/kg/day). For frame of reference, a

standard (b) (4) sucralose, corresponding to (b) (4) in a 70 kg individual. The Kuvan powder formulation contains (b) (4) of sucralose per 100 mg packet. A 70 kg patient will receive (b) (4) of sucralose from dosing of Kuvan powder at 20 mg/kg/day. The US FDA Acceptable Daily Intake for sucralose is 5 mg/kg.

- 4) The study does not contain an assessment of transporter or enzyme activity.

The second publication provided by sponsor contains only an evaluation of the aforementioned animal study by Aboi-Donia et al. No new data or information is presented. With respect to the observed alteration in P-gp/CYP3A4 intestinal protein expression, the authors state that “effects on drug absorption are not expected with sucralose, because it is a simple molecule and has a low potential for chemical reactivity.” However, this does not necessarily negate the potential of sucralose to affect drug transporters and/or metabolic enzymes. It is also stated that “the observed treatment group differences...could have been simply indicative of normal biological variation.” This is highly unlikely given that the variability within treatment and control groups was relatively small. Increases in intestinal CYP3A4 and CYP2D1 expression were dose-dependent and statistically significant, strongly supporting a non-random effect.

A large potential for bias exists in both of these publications. The study by Aboi-Donia et al. was supported by the Sugar Association, Inc. and the report by Brusick et al. was supported by McNeil Nutritionals, LLC, which markets Splenda.

Additional literature

A literature search was conducted on April 4, 2013 to identify additional publications addressing the impact of sucralose on drug absorption and bioavailability. Publications were identified through searches of MEDLINE databases from the period of 1946 to March 2013. The main search terms used were ‘sucralose’ OR ‘Splenda’ combined with any of the following: ‘CYP3A’, ‘cytochrome p450’, ‘P-glycoprotein’, ‘p-gp’, ‘bioavailability’, or ‘absorption’.

No additional published studies were identified. Two authors from the 2008 study describing the effects of Splenda in rats published a rebuttal [Regul Toxicol Pharmacol. 2012 Aug;63(3):505-8] to the critique by Brusick et al. This point-by-point rebuttal addresses each of the critiques raised by Brusick et al and strengthens their assertion that Splenda may alter the protein expression of the efflux transporter P-gp and of two cytochrome P450 isozymes (CYP3A4 and CYP2D1). It is unknown if the Sponsor’s failure to submit this publication represents a deliberate omission.

Other drugs which contain sucralose as an excipient

A search was performed to identify other drugs which contain sucralose as an excipient. The only product identified was intranasal azelastine hydrochloride 0.15% (Astepro, NDA 022371), which contains sucralose as a taste-masking agent. However, considering the route of administration, the pharmacokinetics of this product do not illuminate any potential issues of sucralose to affect absorption in the gastrointestinal tract.

US Patent No. 2006/0121066 A1 was issued on June 8, 2006 for "Sucralose formulations to mask unpleasant tastes". Merck EMD Millipore currently advertises "EMPROVE® Sucralose" as an "innovative sweetener for drugs". However, with the exception of Astepro, no drugs were identified that are currently marketed in the United States and contain sucralose.

Recommendation

Only one study to date provides evidence that sucralose may have an effect on drug absorption and bioavailability via induction of P-glycoprotein and cytochrome p450 enzymes (J Toxicol Environ Health A. 2008;71:1415-29). This animal study has several important limitations, including failure to assess transporter and enzyme activity. Additionally, other components of the marketed Splenda product, such as maltodextrin, were not adequately controlled for. Despite these methodological limitations, the study provides preliminary evidence that sucralose may alter transporter and/or metabolic enzyme expression in the gastrointestinal tract and thus affect bioavailability of drug substrates. No human data is available and further study is necessary.

Biomarin's powder formulation of Kuvan contains (b) (4) of sucralose per dose. This corresponds to (b) (4) of sucralose in a 70 kg patient at 20 mg/kg. The (b) (4) sucralose dose had no effect on intestinal P-gp, CYP3A4, or CYP2D1 protein expression. Additionally, the role of P-gp, CYP3A4, and CYP2D6 in sapropterin disposition are not clear.

Overall, considering the available evidence, the incorporation of sucralose in the Kuvan powder formulation should not prohibit a Biowaiver for this product.

4.4 OCP Filing Form

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology				
<i>New Drug Application Filing and Review Form</i>				
<u>General Information About the Submission</u>				
NDA/BLA Number	Information	205-065	Brand Name	Information
OCP Division (I, II, III, IV, V)	DCP III		Generic Name	Kuvan
Medical Division			Drug Class	sapropterin dihydrochloride
OCP Reviewer	Insook Kim, Ph.D.		Indication(s)	Reduction of phenylalanine levels in patients with hyperphenylalaninemia due to tetrahydrobiopterin-responsive Phenylketonuria
OCP Team Leader	Sue-Chih Lee, Ph.D.		Dosage Form	Powder for oral solution
Pharmacometrics Reviewer			Dosing Regimen	Start at 10 mg/kg/day and adjust doses by blood Phe level in the range of 5-20 mg/kg/day
Date of Submission	February 9, 2013		Route of Administration	Oral
Estimated Due Date of OCP Review			Sponsor	Biomarin
Medical Division Due Date	11/6/2013		Priority Classification	S
PDUFA Due Date	December 6, 2013			
<i>Clin. Pharm. and Biopharm. Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design, single / multi dose:				
replicate design, single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X	2		Two references to support the insignificant effects of sucralose on oral absorption
Total Number of Studies		2		

On initial review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	Biowaiver is requested
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	
5	Has a rationale for dose selection been submitted?			X	

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?			X	
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?			X	
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?			X	
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			X	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

 X

If the NDA/BLA is not fileable from the clinical pharmacology 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.

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Background

Kuvan Tablet (100 mg) is currently on the market. For oral administration, the current Kuvan Tablet should be dissolved in water or apple juice.

The proposed product is a new powder formulation for Kuvan® (sapropterin dihydrochloride) for oral solution. The powder formulation will dissolve completely in water. The sponsor stated that Kuvan powder for oral solution dosage form was developed to facilitate administration of the drug product with various liquids and to offer the benefit of short reconstitution time and solution clarity upon powder dissolution. The sponsor claims that the drug substance in the powder formulation is highly soluble and will rapidly dissolve in the prescribed volume i.e. 4 – 8 oz liquid (118 – 237 mL) of liquids during preparation of dosing solutions. There are no studies conducted in human using the proposed product.

Biowaiver request

The sponsor requested a biowaiver based on the 21 CFR 320.22(b)(3)(i) entitled: "Bioavailability and Bioequivalence (April 2011)", in-vivo 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".

However, the current label states that the tablets may not dissolve completely. The sponsor should provide the evidence of complete dissolution of active ingredient after dissolution of tablet and the powder. The reconstituted concentration should be equivalent. This issue was discussed with the review team including a CMC reviewer and biopharm reviewer on March 19, 2013.

The decision on the necessity of an in vivo BE study is pending and is considered as a review issue for this submission as discussed at a team meeting on March 19, 2013.

Insook Kim, Ph.D.	March 19, 2013
Reviewing Clinical Pharmacologist	Date
Sue-Chih Lee, Ph.D.	March 19, 2013
Team Leader/Supervisor	Date

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

/s/

INSOOK KIM
10/24/2013

SUE CHIH H LEE
10/25/2013

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 205065	Reviewer: Kelly M. Kitchens, Ph.D.	
Submission Date:	February 7, 2013		
Division:	Division of Gastroenterology Drug Products	Acting Team Lead: Tapash Ghosh, Ph.D.	
Applicant:	BioMarin Pharmaceutical Inc.	Acting Supervisor: Richard Lostritto, Ph.D.	
Trade Name:	Kuvan	Date Assigned:	February 18, 2013
Established Name:	Sapropterin Dihydrochloride	Date of Review:	June 3, 2013
Indication:	Reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin-(BH4) responsive Phenylketonuria (PKU).	Type of Submission: New Drug Application 505(b)(1)	
Formulation/ strengths	Powder for oral solution		
Route of Administration	Oral		
Type of Review:	Review of dissolution data to support biowaiver request		
<u>SUMMARY:</u>			
<p>Background: BioMarin currently markets an approved Kuvan (sapropterin dihydrochloride) Tablet, 100 mg, under NDA 022181 (approved December 13, 2007). Kuvan Tablets should be dissolved in 4 – 8 oz. (120 – 140 mL) of water or apple juice and taken within 15 minutes of dissolution. Kuvan tablets are administered orally with food to increase absorption. BioMarin has developed a new powder formulation for administration as an oral solution to be packaged in a unit dose packet. 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.</p> <p>The Applicant submitted the current NDA to seek approval for Kuvan (sapropterin dihydrochloride) Powder for Oral Solution. A Type C meeting was held on June 21, 2012 to discuss the biowaiver of in vivo bioavailability and bioequivalence studies for Kuvan Powder.¹ In response to the Applicant's query if Kuvan Powder is eligible for a biowaiver, the FDA requested the Applicant submit information/justification to address the following concerns:</p>			
<ol style="list-style-type: none"> 1. There is evidence in the scientific literature, although not totally conclusive, that sucralose 			

¹ DARRTS: NDA 022181, TRAN-ZWANETZ, CATHERINE A, Submit/Final Date: 07/20/2012, COR-MEET-03(Meeting Minutes)

may potentially affect the absorption and bioavailability of drugs (Abou-Donia et al. 2008, Brusick et al. 2009). This may apply to your product depending on the elimination pathway of sapropterin dihydrochloride.

2. Your proposed product (after it is dissolved in water or apple juice) may have a markedly different osmolarity compared to the reference product, potentially impacting the bioavailability of sapropterin dihydrochloride.

Discussion from Type C meeting: Based on new data/information provided in the sponsor's response, FDA believes a biowaiver may be granted. However, final determination of the acceptance of the biowaiver will be made during the review of the NDA. FDA stated that the sponsor should include these data/information (response to bullet point numbers 1 and 2 above) as well as solubility data for the API and dissolution profile data for the proposed product in their NDA submission.

Submission: The Applicant requested a biowaiver for the Kuvan powder formulation per 21 CFR 320.22 (b)(3)(i), and per the Type C meeting for NDA 022181, Kuvan (sapropterin dihydrochloride) Tablets (June 21, 2012).

Review: The Biopharmaceutics review summarizes the information supporting the biowaiver request, and makes conclusions and recommendations about the biowaiver request.

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

1. The powder formulation delivers an identical quantity of active pharmaceutical ingredient and ^{(b)(4)} levels of 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 205065 for Kuvan (sapropterin dihydrochloride) Powder for Oral Solution is recommended for approval.

Signature

Kelly M. Kitchens, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Signature

Tapash Ghosh, Ph.D.
Acting Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

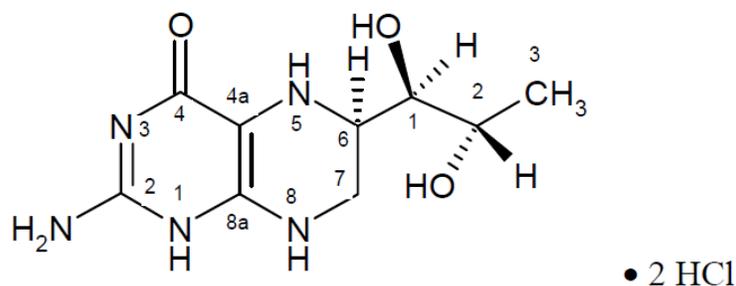
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BIOPHARMACEUTICS ASSESSMENT

Drug Substance:

Sapropterin dihydrochloride is an off-white to light yellow crystalline powder. The chemical structure of sapropterin dihydrochloride is:

6R Form (Active) – 4(1H) Conformation



Drug Product:

Kuvan (sapropterin dihydrochloride) Tablets, 100 mg, are currently marketed to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH₄) responsive Phenylketonuria (PKU). Kuvan is used in conjunction with a Phe-restricted diet. Kuvan Tablets were filed under NDA 22181 and approved on December 13, 2007. The Applicant 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. The powder formulation comprises ingredients that dissolve completely in water and offers the benefit of short reconstitution time and solution clarity upon powder dissolution.

Kuvan powder is packaged in an individual, two inch square, white, printed, multi-layered, (b)(4) laminate packet which is heat sealed on four sides. An internal tear notch is located in the corner of the packet to facilitate opening the (b)(4) (b)(4) container. Each packet contains 100 mg active pharmaceutical ingredient sapropterin dihydrochloride, equal to 76.8 mg sapropterin. The target fill weight for each packet is (b)(4). Thirty packets are placed into a carton along with the package insert. The compositions for Kuvan Powder and Kuvan Tablet formulations are described in the following table:

Ingredient	Kuvan Powder Formulation for Oral Solution		Kuvan Tablet	
	%	Amount per packet (mg)	%	Amount per tablet (mg)
Sapropterin dihydrochloride	(b) (4)	100.0	(b) (4)	100.00
Mannitol	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Crospovidone	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Dibasic Calcium Phosphate	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Riboflavin	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sodium Stearyl Fumarate	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sucralose	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Potassium Citrate	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Ascorbic acid	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Total	100.0%		100.00%	

Biowaiver Request:

The Applicant provided the following justifications to support the biowaiver request:

1. **Composition:** Each dose unit of the tablet and powder formulations (tablet or packet, respectively) delivers an identical quantity of active pharmaceutical ingredient and (b) (4) levels of the primary excipient, mannitol.
2. **Solubility:** Sapropterin dihydrochloride is very soluble in aqueous solutions exhibiting solubility greater than 1 g/mL in water, (b) (4) solutions. Like the currently marketed Kuvan tablet formulation, the powder formulation is intended to be pre-dissolved or constituted in aqueous liquid prior to oral administration.

The following table summarizes the results of tests performed per pharmacopoeial methods to examine the solubility of sapropterin dihydrochloride in various solvents. For each test, a powdered sample was placed in the solvent at 20°C ± 5°C. The sample was vigorously shaken for 30 seconds every five minutes, until the solubility was determined after 30 minutes.

Solubility of Sapropterin Dihydrochloride in Various Solvents (Temperature 20°C)

Solvent	Solvent required for 1 g of solute	Solubility
Water	Less than 1 mL	Very soluble
(b) (4)	(b) (4)	Very soluble
		Very soluble
		Sparingly soluble
		Very slightly soluble
		Practically insoluble

T.S. = test solution

3. **Dissolution:** The Applicant conducted a dissolution study on the Kuvan Powder formulation using the approved dissolution method for Kuvan Tablets (USP apparatus II at 50 rpm, 900 mL 0.1N HCl at 37°C). The following potential review issues were submitted to the Applicant on April 22, 2013, in the 74-day letter:
1. Please submit the complete dissolution data for Kuvan (sapropterin dihydrochloride) Powder for oral solution, which include the individual data, mean, % CV, dates of dissolution testing, and dissolution profiles.
 2. Please submit the dissolution method validation report for the Kuvan powder drug product.

On May 8, 2013, the Applicant submitted the following responses to the 74-day letter:

Response to comment #1:

Dissolution profile results demonstrating high solubility of the dosage form (complete dissolution in less than 5 minutes) were provided as Figure 3.2.P.2.2.3.1 in Section 2.P.2.2.3 of the NDA. The figure is reproduced below:

**Dissolution Profile*, Sapropterin Dihydrochloride, Powder for Oral Solution,
Batch (b) (4)%SAP-052012**



Note: *Dissolution profile generated using the USP method (apparatus II, 50 RPM, 900 mL 0.1 N HCl at 37°C)

These data are supplemented with the other requested information in [Table 1](#).

Table 1: Dissolution Profile Test Data for Batch (b) (4) %SAP-052012, Generated 9 November 2012

Replicate	Measured Sapropterin Dihydrochloride Concentration (mg/mL)							
	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min
1	(b) (4)							
2								
3								
4								
5								
Average	0.118	0.118	0.118	0.119	0.120	0.120	0.119	0.120
STD	0.002	0.002	0.003	0.002	0.002	0.002	0.003	0.003
CV	1.8%	2.0%	2.5%	1.8%	2.1%	2.0%	2.2%	2.2%
%Dissolution¹	(b) (4)							

¹ Calculated relative to a 100-mg/packet label claim; the measured assay for batch (b) (4) %SAP-052012 was (b) (4) packet.

Response to comment #2:

The validation of the measurement of sapropterin dihydrochloride concentration in solution is described in [Validation Report QC-996-A](#), supplied with the NDA. Validation of the concentration measurement supports its use for determining assay, content and blend uniformity, and for assessing dissolution characteristics.

Reviewer’s comments to Applicant’s response to comment #2: The applicant submitted the validation of the content uniformity test method, but did not submit the validation of the dissolution test method. The Reviewer located the dissolution method validation report for Kuvan (sapropterin dihydrochloride) Tablets in NDA 22181. The validation results of the dissolution method used for Kuvan Powder are summarized in the following table:

Parameters	Data
Source of Data	Method Validation of Dissolution Rate for 100 mg Rapid Dissolved (b) (4) Tablets Protocol No. (b) (4) Issue Date: July 1, 2005
Linearity/Range	44, 66, 88, 110, 121, and 143 µg/mL R = 1.00
Accuracy/Recovery	At 80% level: 100.4% At 100% level: 100.8% At 120% level: 101.2%
Precision: Method Repeatability	%RSD (n=6): 0.5%
Precision: Intermediate Precision	Analyst 1 %RSD (n=6): 0.5% Analyst 2 %RSD (n=6): 0.7% Overall %RSD (n=12): 0.8% 1.0% difference between mean (b) (4) dissolution
Specificity	No interfering peaks observed for standard, placebo, and

	dissolution medium
Standard Solution Stability	8 hours at 5°C
Sample Solution Stability	8 hours at 5°C
Filter Compatibility	(b) (4)
Robustness	% mean release (n=6) at 15 min using deaerated medium: 103% % mean release at (n=6) 15 min using non-deaerated medium: 103% % difference between deaerated and non-deaerated medium: 0.0%
HPLC Assay	Column: (b) (4) Column Temp: 40°C ± 2°C Mobile Phase: 30 mM ammonium dihydrogenphosphate, 3 mM ammonium sulfate Flow rate: 1.5 mL/min Injection volume: 10 µL Detection: 265 nm Run Time: 7.5 minutes Autosampler temperature: 4°C

***Reviewer’s Note:** In the cover letter for the original submission of NDA 22181 (May 25, 2007), the Applicant indicated “Over the course of the development program the drug product was at times referred to (b) (4), “sapropterin”, “sapropterin hydrochloride” and “sapropterin dihydrochloride”. This nomenclature has been used in many of the NDA documents submitted herein and all of these names are equivalent to Sapropterin Dihydrochloride 100 mg Tablets unless otherwise indicated.”

4. **Osmolarity:** The following table demonstrates that Kuvan Powder has similar osmolarity as Kuvan Tablets in water and apple juice, liquids used to dissolve the drug products prior to oral administration:

Test Run	2 Kuvan tablets or Packets dissolved in 20 ml water		2 Kuvan tablets or Packets dissolved in 20 ml Apple juice	
	Tablets (mOsm/kg)	Packets (mOsm/kg)	Tablets (mOsm/kg)	Packets (mOsm/kg)
1	207	229	941	970
2	208	224	949	978
3	206	226	948	980
Average	207	226	946	976

5. **21 CFR 320.22(b)(3)(i):** The proposed drug product is a powder for oral solution, contains an active ingredient in the same concentration and dosage form (i.e. oral solution) as approved Kuvan Tablets, and does not contain an inactive ingredient that may significantly affect absorption of the active ingredient.

- Mannitol, the excipient that is present in both the tablet and powder formulation, is present at lower levels in the powder formulation compared to the approved tablet formulation.
- Sucralose has also been reported to potentially affect drug absorption and bioavailability. The Applicant references research articles by Abou-Donia et al. (2008), Brusick et al. (2009), and Davis et al. (1987) to suggest that

the proposed amount of sucralose in the powder formulation ((b) (4)) does not affect drug absorption and bioavailability.

- Based on a maximum daily dose of 20 mg/kg, the maximum daily dose of sucralose in the powder formulation corresponds to (b) (4) (b) (4). Abou-Donia et al. reported in vivo evidence that a sucralose dose of (b) (4) did not affect the levels of P-gp, CYP3A4, and CYP2D1. At this sucralose dose decreased beneficial intestinal bacteria, increased fecal pH, and increased body weight were observed, and these adverse events remained after 12-week recovery. These adverse events were also observed at higher sucralose doses (3.3 – 5.5 mg/kg/day), as well as increased expression of P-gp, CYP3A4, and CYP2D1. At 11 mg/kg/day, decreased P-gp and increased CYP3A4, and CYP2D1 levels were observed. The Applicant suggests that since the amount of sucralose in the Kuvan powder formulation (b) (4) (b) (4) is comparable to the amount of sucralose that did not affect P-gp, CYP3A4, and CYP2D1 expression in vivo ((b) (4) (b) (4)), the sucralose will not affect the absorption and bioavailability of sapropterin dihydrochloride.
- Brusick et al. reported that the conclusions reached by Abou-Donia et al. are not scientifically valid, and are inconsistent with published literature. Studies have shown that ~85% of an oral dose of sucralose is unabsorbed, and rapidly excreted, protein binding of sucralose has not been observed, and a study with high doses of sucralose (7.5 mg/kg/day for 3 months) were not associated with any changes in diabetic therapeutic regimens. Although Brusick et al. point out deficiencies in the study design and methodology conducted by Abou-Donia et al., Brusick et al. suggests that sucralose does not affect drug absorption.
- Per Davis et al., sapropterin dihydrochloride is prone to rapid auto-oxidation in-vitro, and is rapidly eliminated via an oxidative pathway to 7, 8 dihydrobiopterin (BH2) and biopterin (B) in-vitro at buffer pH comparable to plasma pH. The Applicant suggests that cytochrome isoenzymes are unlikely to be involved in the elimination pathway for sapropterin dihydrochloride due to its rapid auto-oxidation.
- The Pharm/Tox reviewer, Dr. Yuk-Chow Ng, agreed that the amount of sucralose in the powder formulation is acceptable and is not expected to affect drug absorption and bioavailability.

Overall Conclusions:

- The Kuvan powder formulation contains the same active ingredient in the same concentration as the Kuvan tablet formulation.
- Kuvan Powder is highly soluble in aqueous solution.
- Kuvan Powder exhibits rapid dissolution (i.e. (b) (4) % dissolved in 5 minutes) using the dissolution method for Kuvan Tablets.

- Kuvan Powder has similar osmolarity as Kuvan Tablets in water and apple juice.
- The inactive ingredients in the powder formulation are not expected to affect drug absorption and bioavailability.
- The amount of sucralose in the powder formulation is acceptable and is not expected to affect drug absorption and bioavailability.
- The waiver for in-vivo bioavailability/bioequivalence studies is granted.

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 205065 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/

KELLY M KITCHENS
10/07/2013

TAPASH K GHOSH
10/08/2013

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	205-065	Brand Name	Kuvan
OCP Division (I, II, III, IV, V)	DCP III	Generic Name	sapropterin dihydrochloride
Medical Division		Drug Class	
OCP Reviewer	Insook Kim, Ph.D.	Indication(s)	Reduction of phenylalanine levels in patients with hyperphenylalaninemia due to tetrahydrobiopterin-responsive Phenylketonuria
OCP Team Leader	Sue-Chih Lee, Ph.D.	Dosage Form	Powder for oral solution
Pharmacometrics Reviewer		Dosing Regimen	Start at 10 mg/kg/day and adjust doses by blood Phe level in the range of 5-20 mg/kg/day
Date of Submission	February 9, 2013	Route of Administration	Oral
Estimated Due Date of OCP Review		Sponsor	Biomarin
Medical Division Due Date		Priority Classification	
PDUFA Due Date	December 6, 2013		

Clin. Pharm. and Biopharm. Information

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X	2		Two references to support the insignificant effects of sucralose on oral absorption
Total Number of Studies		2		

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	Biowaiver is requested
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	
5	Has a rationale for dose selection been submitted?			X	

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?			X	
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?			X	
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?			X	
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			X	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

 X

If the NDA/BLA is not fileable from the clinical pharmacology 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.

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Background

Kuvan Tablet (100 mg) is currently on the market. For oral administration, the current Kuvan Tablet should be dissolved in water or apple juice.

The proposed product is a new powder formulation for Kuvan® (sapropterin dihydrochloride) for oral solution. The powder formulation will dissolve completely in water. The sponsor stated that Kuvan powder for oral solution dosage form was developed to facilitate administration of the drug product with various liquids and to offer the benefit of short reconstitution time and solution clarity upon powder dissolution. The sponsor claims that the drug substance in the powder formulation is highly soluble and will rapidly dissolve in the prescribed volume i.e. 4 – 8 oz liquid (118 – 237 mL) of liquids during preparation of dosing solutions. There are no studies conducted in human using the proposed product.

Biowaiver request

The sponsor requested a biowaiver based on the 21 CFR 320.22(b)(3)(i) entitled: “Bioavailability and Bioequivalence (April 2011)”, in-vivo 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”.

However, the current label states that the tablets may not dissolve completely. The sponsor should provide the evidence of complete dissolution of active ingredient after dissolution of tablet and the powder. The reconstituted concentration should be equivalent. This issue was discussed with the review team including a CMC reviewer and biopharm reviewer on March 19, 2013.

The decision on the necessity of an in vivo BE study is pending and is considered as a review issue for this submission as discussed at a team meeting on March 19, 2013.

Insook Kim, Ph.D.	March 19, 2013
Reviewing Clinical Pharmacologist	Date
Sue-Chih Lee, Ph.D.	March 19, 2013
Team Leader/Supervisor	Date

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

/s/

INSOOK KIM
04/04/2013

SUE CHIH H LEE
04/04/2013