CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204553Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	204-553
Submission Date:	11/30/2012
Trade Name	(b) (4)
Active Ingredient	Sodium sulfate, potassium sulfate, magnesium sulfate
Dosage Forms/Strength	Sodium sulfate: 17.5 g, potassium sulfate 3.13 g and magnesium sulfate 1.6 g Split Dose (2-Day) Regimen • Evening before colonoscopy: Take ONE (1) bottle containing 22.7 g (b) (4) for Oral Solution Kit and add water up to the neck of the bottle. Shake well and mix thoroughly. Pour the contents of one bottle of reconstituted solution into the mixing container provided. Fill the container with water to the 16 oz fill line, and drink the entire amount. • Drink 32 oz water over the next hour. • Next morning: repeat both steps using the second bottle. • Complete preparation at least 2 hours before colonoscopy.
Indication	For cleansing of the colon as a preparation for colonscopy in adults
Sponsor	Gator Pharmaceuticals
Type of Submission	Original
Reviewer	Insook Kim, Ph.D.
Team Leader	Sue-Chih Lee, Ph.D.

Executive Summary

This is a 505(b)(2) submission with the listed drug SUPREP (NDA # 022-372) as a reference product. The proposed product is a powder mixture of sodium sulfate, potassium sulfate and magnesium sulfate and the product is proposed to be reconstituted in 16 oz of water before oral administration. No clinical trials were conducted using (b) (4) and the proposed labeling relies on the labeling of SUPREP BOWEL PREP (sodium sulfate, potassium sulfate, magnesium sulfate) solution, concentrate**.** The sponsor requested for a waiver of in-vivo bioequivalence requirement.

The sponsor requested a biowaiver based on the provision of 21 CFR 320.22 (b) (3). Although the dosage forms are different i.e. powder for the proposed product versus solution for the reference product, two products will be administered as oral solution with the same final concentrations of each active ingredient after reconstitution to the final solution. The each ingredient can be completely dissolved from the (b) (4) prior to oral administration; therefore the difference in the dosage forms prior to reconstitution is not expected to affect the oral bioavailability.

The final concentration of each component in reconstituted solution of [redacted] (b) (4) is to be the same as in the diluted Suprep Solution (Table 1).

Table 1. Formulation comparison between [redacted] (b) (4) and SUPREP Bowel Prep

	[redacted] (b) (4)	SUPREP Bowel Prep Kit
Dosage form	two 22.7 g bottles of powder	two 6 oz bottles of solution
Active ingredient	sodium sulfate 17.5 g potassium sulfate 3.13 g magnesium sulfate 1.6 g	sodium sulfate 17.5 g potassium sulfate 3.13 g magnesium sulfate 1.6 g
Inactive ingredient	sucralose citric acid	sodium benzoate sucralose malic acid citric acid
Final volume after reconstitution	16 oz	16 oz

Recommendation

The Division of Clinical Pharmacology 3 has reviewed this submission and found acceptable from a clinical pharmacology standpoint. Following labeling comments should be conveyed to the sponsor.

Labeling comments:

We recommend following revisions to the labeling for further clarity. Major recommended change is to create a subheading of "Specific populations"s under Section 12.3 Pharmacokinetics.

Proposed labeling	Recommended revisions
[redacted] (b) (4)	After administration of [redacted] (b) (4) sodium sulfate, potassium sulfate, and magnesium sulfate in six healthy volunteers, the time at which serum sulfate reached its highest point (Tmax) was approximately 17 hours after the first half dose or approximately 5 hours after the second dose, and then declined with a half-life of 8.5 hours. Fecal excretion was the primary route of sulfate elimination.
	Specific populations **Hepatic and renal impairment** The disposition of sulfate after administration of [redacted] (b) (4) was

[redacted] (b) (4)	also studied in patients (N=6) with mild-moderate hepatic impairment (Child-Pugh grades A and B) and in patients (N=6) with moderate renal impairment (creatinine clearance of 30 to 49 mL/min). The renal impairment group had the highest serum sulfate AUC and Cmax, followed by the hepatic impairment group, and then by healthy subjects. The mean sulfate levels of all three groups returned to their respective baseline levels by Day 6 after dose initiation. Systemic exposure of serum sulfate (AUC and Cmax) was similar between healthy subjects and hepatic impairment patients. Urinary excretion of sulfate over 30 hours, starting after the first half dose, was similar between hepatic patients and normal volunteers.
	In patients with moderate renal impairment, [redacted] (b) (4) mean AUC and Cmax was 54% [redacted] (b) (4) and 44% higher [redacted] (b) (4) than those in healthy subjects, respectively. Urinary excretion of sulfate over 30 hours, starting after the first half dose, was approximately 16% lower in moderate renal impairment patients than in healthy volunteers.

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/s/

INSOOK KIM
08/20/2013

SUE CHIH H LEE
08/21/2013

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	**204-553**	**Brand Name**	(b) (4)
OCP Division (I, II, III, IV, V)	**III**	**Generic Name**	Sodium sulfate, Potassium sulfate and Magnesium sulfate
Medical Division	**DGIEP**	**Drug Class**	**Bowel Preparation Agent**
OCP Reviewer	**Insook Kim, Ph.D.**	**Indication(s)**	for cleansing of the colon as a preparation for colonscopy in adults.
OCP Team Leader	**Sue-Chih Lee, Ph.D.**	**Dosage Form**	**Powder**
Pharmacometrics Reviewer		**Dosing Regimen**	**Split dose**
Date of Submission	**11/30/2012**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review		**Sponsor**	**Gator Pharmaceuticals**
Medical Division Due Date		**Priority Classification**	**S**
PDUFA Due Date	**10/4/2013**		

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:				

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

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multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
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				
Total Number of Studies	**0**			

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		See filing memo as below
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?		x		See filing memo as below
4	Did the sponsor submit data to allow the evaluation of the validity			x	

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	of the analytical assay?				
5	Has a rationale for dose selection been submitted?			x	
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	

Filing Memo

This is a 505(b)(2) submission with the listed drug SUPREP (NDA # 022-372) as a reference product. The proposed product is a powder mixture of sodium sulfate, potassium sulfate and magnesium sulfate and the product is proposed to be reconstituted in 16 oz of water before administration per oral. The final concentration of each component in reconstituted solution is to be the same as in the diluted Suprep Solution (Table 1).

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The sponsor requested for a waiver of in-vivo bioequivalence requirement. Although the dosage forms are different i.e. powder versus solution, two products will be reconstituted to the same final concentrations of each active ingredient in solution. Provided the each ingredient can be completely dissolved from the (b) (4) prior to oral administration, the difference in dosage forms is not expected to affect the oral bioavailability. As such a bioequivalence study between the proposed product and the reference listed product is not be needed according to the provisions 21 CFR 320.22 (b) (3).

No clinical pharmacology related studies were submitted for our review and the proposed labeling relies on the labeling of Suprep.

Table 1. Formulation comparison between (b) (4) and SUPREP Bowel Prep Kit

	(b) (4)	SUPREP Bowel Prep Kit
Dosage form	two 22.7 g bottles of powder	two 6 oz bottles of solution
Active ingredient	sodium sulfate 17.5 g potassium sulfate 3.13 g magnesium sulfate 1.6 g	sodium sulfate 17.5 g potassium sulfate 3.13 g magnesium sulfate 1.6 g
Inactive ingredient	sucralose citric acid	sucralose citric acid malic acid sodium benzoate
Final volume after reconstitution	16 oz	16 oz

21 CFR 320.22 (b) (3)

(3) The drug product:

(i) Is a solution for application to the skin, an oral solution, elixir, syrup, tincture, a solution for aerosolization or nebulization, a nasal solution, or similar other solubilized form; and

(ii) Contains an active drug ingredient in the same concentration and dosage form as a drug product that is the subject of an approved full new drug application or abbreviated new drug application; and

(iii) Contains no inactive ingredient or other change in formulation from the drug product that is the subject of the approved full new drug application or abbreviated new drug application that may significantly affect absorption of the active drug ingredient or active moiety for products that are systemically absorbed, or that may significantly affect systemic or local availability for products intended to act locally.

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
__Yes_____

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.

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Insook Kim, Ph.D.	February 1, 2013
Reviewing Clinical Pharmacologist	Date
Sue-Chih Lee, Ph.D.	February 1, 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
01/31/2013

SUE CHIH H LEE
01/31/2013