CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204553Orig1s000

NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	204553
Supporting document/s:	006
eCTD Sequence number:	0005
Submission Category:	Resubmission/Class 1 (Type 3)
Applicant's letter date:	November 30, 2012
CDER stamp date:	December 4, 2012
Product:	(b) (4) (Sodium Sulfate, Potassium Sulfate, Magnesium Sulfate)
Indication:	(b) (4) is an osmotic laxative indicated for cleansing of the colon in preparation for colonoscopy in adults
Applicant:	Gator Pharmaceuticals, Inc.
Review Division:	DGIEP
Reviewer:	Tamal K. Chakraborti, Ph.D.
Supervisor:	Sushanta K. Chakder, Ph.D.
Division Director:	Donna Griebel, MD
Project Manager:	Matthew Scherer, MBA

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 204553 are owned by Gator Pharmaceuticals, Inc. or are data for which Gator Pharmaceuticals, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 204553 that Gator Pharmaceuticals, Inc. 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 204553.

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1 Executive Summary

1.1 Introduction

The Applicant has submitted this NDA as a re-submission of the Original 505(b)(2) application seeking marketing approval for [redacted] (b) (4) (sodium sulfate, potassium sulfate, and magnesium sulfate). The original NDA was submitted on August 2, 2012 as a 505(b)(2) application. During the preliminary review of the original submission, Chemistry Manufacturing Control (CMC) deficiencies were identified (Division letter dated October 3, 2012). The original NDA was withdrawn by the Applicant on September 27, 2012. The Applicant referred to Suprep® Bowel Prep Kit (Braintree Laboratories, Inc., NDA 22372) as the reference listed drug (RLD).

1.2 Brief Discussion of Nonclinical Findings

N/A

1.3 Recommendations

1.3.1 Approvability

From a nonclinical standpoint, this NDA is recommended for approval.

1.3.2 Additional Non Clinical Recommendations

N/A

1.3.3 Labeling

The draft labeling of [redacted] (b) (4) conforms to the specific requirements on content and format of labeling for human prescription drugs under 21CFR201.57. Overall, the nonclinical sections of the label appear to be appropriate and acceptable and are discussed below.

8.1 Pregnancy

Applicant's Version:

"**8.1 Pregnancy**

Teratogenic effects: Pregnancy Category C.

Animal reproduction studies have not been conducted with [redacted] (b) (4) It is also not known whether [redacted] (b) (4) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. [redacted] (b) (4) should be given to a pregnant woman only if clearly needed."

Evaluation: The text of the label appears to be appropriate and acceptable.

Recommended Version: N/A

8.3 Nursing Mothers

Applicant's Version:

"**8.3 Nursing Mothers**

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when (b) (4) is administered to a nursing woman."

Evaluation: The text of the label appears to be appropriate and acceptable.

Recommended Version: N/A

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Applicant's Version:

"**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of (b) (4) Studies to evaluate the possible impairment of fertility or mutagenic potential of (b) (4) have not been performed."

Evaluation: The text of the label appears to be appropriate and acceptable.

Recommended Version: N/A

13.2 Animal Toxicology and/or Pharmacology

Applicant's Version:

13.2 Animal Toxicology and/or Pharmacology

The sulfate salts of sodium, potassium, and magnesium contained in (b) (4) were administered orally (gavage) to rats and dogs up to 28 days up to a maximum daily dose of 5 g/kg/day (approximately 0.9 and 3 times for rats and dogs, respectively, the recommended human dose of 44 g/day or 0.89 g/kg based on the body

surface area). In rats, the sulfate salts caused diarrhea and electrolyte and metabolic changes, including hypochloremia, hypokalemia, hyponatremia, lower serum osmolality, and high serum bicarbonate. Significant renal changes included increased fractional sodium excretion, increased urinary sodium and potassium excretion, and alkaline urine in both males and females. In addition, creatinine clearance was significantly decreased in females at the highest dose. No microscopic renal changes were seen. In dogs, the sulfate salts caused emesis, excessive salivation, excessive drinking of water, and abnormal excreta (soft and/or mucoid feces and/or diarrhea) and increased urine pH and sodium excretion.

Evaluation: The text of the label appears to be appropriate and acceptable.

Recommended Version: N/A

2 Drug Information

2.1 Drug

Generic Name: Sodium sulfate, potassium sulfate and magnesium sulfate powder for oral solution

Chemical Name: Sodium sulfate, potassium sulfate and magnesium sulfate

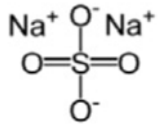
Molecular Formula/Molecular Weight: The following (from the Section 2.3.S. of the original submission) shows the details of sodium sulfate, potassium sulfate and magnesium sulfate.

Sodium sulfate, anhydrous:

Chemical Name: Sodium sulfate

CAS#: [7757-82-6]

Structural Formula:



Molecular Formula: Na_2SO_4

Molecular Weight: 142.04

Potassium sulfate, anhydrous:

Chemical Name: Potassium sulfate

CAS#: [7778-80-5]

Structural Formula:

Molecular Formula: K_2SO_4

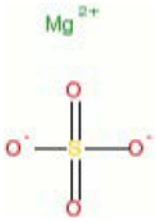
Molecular Weight: 174.26

Magnesium sulfate, anhydrous:

Chemical Name: Magnesium sulfate

CAS#: [7487-88-9]

Structural Formula:



Molecular Formula: $MgSO_4$

Molecular Weight: 120.37

Pharmacologic Class: Osmotic laxative

2.2 Relevant IND/s, NDA/s, and DMF/s

1. PIND 113084 ((b) (4) KVK-Tech, Inc.)
2. NDA 22372 (Suprep Bowel Prep Kit (Braintree Laboratories, Inc.)

2.3 Drug Formulation

(b) (4) contains sodium sulfate (17.5 g), potassium sulfate (3.13 g), and magnesium sulfate (1.6 g). The drug product is a powder mixture of the above

components and to be reconstituted with water prior to oral administration. It is an immediate release solution upon reconstitution. Sodium sulfate (b) (4) (b) (4) Potassium sulfate ((b) (4) %) and magnesium sulfate ((b) (4) %) are mixed together with citric acid (b) (4) (b) (4) sucralose (b) (4) and lemon flavor. The following table shows the composition of the drug product.

i. **Batch Formulation:**

Batch Number	QC/PD/065/013	
Batch Size	(b) (4)	
Ingredients	Amount per Bottle (gm)	Quantity Required (gm)
Part A		
Sodium Sulfate Anhydrous USP	17.5	(b) (4)
Part B		
Potassium sulfate, Anhydrous, FCC	3.13	
Magnesium sulfate, Anhydrous, USP	1.6	
Citric Acid, Anhydrous, USP	(b) (4)	
Sucralose, USP		
Lemon Flavor		
Total		

2.4 Comments on Novel Excipients

The excipients were similar to the excipients present in the referenced drug product Suprep Bowel Prep Kit. The excipients are shown in the Table below (from page 4 of Section 2.3.P.2.2). All excipients (except flavor) are USP/NF grade.

Excipients	Function
Citric Acid Anhydrous, USP	(b) (4)
Sucralose, USP	
Lemon Flavor	

2.5 Comments on Impurities/Degradants of Concern

The following table (from the sponsor's CMC submission) shows the drug product release specifications.

KVK-TECH, INC.

DRUG PRODUCT RELEASE SPECIFICATION

Product Name: (b) (4)

MOA #: **083** Revision #: **08** Effective Date: **06/27/2013**

Specification: **USP / In-house**

No.	Test	Specification
1.	Description:	White to off white granular powder
2.	Identification: A (Sodium <191>)	Must comply
	Identification: B (Potassium <191>)	Must comply
	Identification: C (Magnesium <191>)	Must comply
	Identification: D (Sulfate <191>)	Must comply
3.	Assay: For Sodium	(b) (4)%
	Assay: For Potassium	(b) (4)%
	Assay: For Magnesium	(b) (4)%
	Assay: For Total sulfates	(b) (4)%
4.	(b) (4)	NMT (b) (4)%
5.	Uniformity of dosage unit: (Content Uniformity) <905>	
	For Sodium	Acceptance Value NMT (b) (4)
	For Potassium	Acceptance Value NMT (b) (4)
	For Magnesium	Acceptance Value NMT (b) (4)
6.	pH for the reconstitution solution:	NLT (b) (4)

KVK-TECH, INC.

DRUG PRODUCT RELEASE SPECIFICATION

Product Name: (b) (4)

MOA #: **083** Revision #: **08** Effective Date: **06/27/2013**

Specification: **USP / In-house**

No.	Test	Specification
7		(b) (4)

The Applicant was asked by the CMC team to set the limits of the elemental impurities as per the USP <232>. All the elemental impurities are below the USP <232> limits. The estimated daily exposure to (b) (4) from (b) (4) g/day dose of the drug product at NMT (b) (4) ppm would be (b) (4) µg/day which is below the USP limit of 25 µg/day. In addition, the drug product will be administered only in two doses as a split dose (2-day) regimen as follows: one dose (22.7 g) in the evening before the day of the colonoscopy and the second dose (22.7 g) in the next morning on the day of the colonoscopy. Therefore, the

proposed specification of (b) (4) at NMT (b) (4) ppm in the drug product does not appear to raise any safety concern from the nonclinical perspective and is acceptable.

2.6 Proposed Clinical Population and Dosing Regimen

(b) (4) is an osmotic laxative indicated for cleansing of the colon in preparation for colonoscopy in adults. The drug product will be administered as a split dose (2-day) regimen as follows: one dose (22.7 g) in the evening before the day of the colonoscopy and the second dose (22.7 g) in the next morning on the day of the colonoscopy.

2.7 Regulatory Background

The PIND 113084 (KVK-Tech, Inc.) meeting request was submitted on August 9, 2011 to discuss the requirements for submission of a 505(b)(2) NDA. The Type B meeting was scheduled on December 7, 2011, which was cancelled on December 2, 2011 as the Division's preliminary responses (meeting preliminary comments dated November 16, 2011) adequately answered the sponsor's questions and, therefore, a meeting was no longer necessary.

The original NDA was submitted on August 2, 2012 as a 505(b)(2) application. There were Chemistry Manufacturing Control (CMC) deficiencies in the original NDA. The original NDA was subsequently withdrawn by the Applicant on September 27, 2012. The Applicant has now submitted this NDA as a re-submission of the Original 505b(2) application referring to Suprep® Bowel Prep Kit (Braintree Laboratories, Inc., NDA 22372) as the RLD.

3 Studies Submitted

The Applicant did not submit any nonclinical study report in this submission and referred to NDA 22372 (Suprep, Braintree Laboratories, Inc.).

3.1 Studies Reviewed

N/A

3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

Pharmacology review of NDA 22372 (Suprep, Braintree Laboratories, Inc.) dated March 6, 2009.

4 Pharmacology

4.1 Primary Pharmacology

N/A

4.2 Secondary Pharmacology

N/A

4.3 Safety Pharmacology

N/A

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

N/A

5.2 Toxicokinetics

N/A

6 General Toxicology

6.1 Single-Dose Toxicity

N/A

6.2 Repeat-Dose Toxicity

N/A

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

N/A

7.2 *In Vitro* Assays in Mammalian Cells

N/A

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

N/A

7.4 Other Genetic Toxicity Studies

N/A

8 Carcinogenicity

N/A

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

N/A

9.2 Embryonic Fetal Development

N/A

9.3 Prenatal and Postnatal Development

N/A

10 Special Toxicology Studies

N/A

11 Integrated Summary and Safety Evaluation

(b) (4) is similar to Suprep® (approved in August 2010 under NDA 022372). (b) (4) is an osmotic laxative indicated for cleansing of the colon in preparation for colonoscopy in adults. Suprep is a liquid formulation, while (b) (4) is a powder formulation containing the same active ingredients used in Suprep, which needs to be reconstituted in water prior to ingestion. The dissolved (b) (4) will contain the same active ingredients in the same concentrations as Suprep.

The Division agreed (meeting preliminary comments dated November 16, 2011) with the KVK-Tech's (PIND 113084) that no nonclinical studies will be required for the 505(b)(2) NDA submission:

This NDA is a re-submission of the Original 505(b)(2) NDA. In the current application, the Applicant did not submit any nonclinical study report and referred to NDA 22372 (Suprep, Braintree Laboratories, Inc.). As mentioned before, (b) (4) contains the same active ingredients in the same concentrations as Suprep. Please refer to pharmacology review of NDA 22372 (Suprep, Braintree Laboratories, Inc.) dated March 6, 2009 for nonclinical review. From a nonclinical standpoint, this NDA is recommended for approval.

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/

TAMAL K CHAKRABORTI
08/16/2013

SUSHANTA K CHAKDER
08/16/2013

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 204553 **Applicant: Gator Pharmaceuticals, Inc.** **Stamp Date: 8/3/12**

Drug Name: [redacted] (b) (4) **NDA Type: New 505(b)(2) NDA** **Submit Date: 8/2/12**

(sodium sulfate, potassium sulfate and magnesium sulfate) 17.5 g/3.13 g/1.6 g per bottle

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?			This is a 505b2 application that references NDA 22372 (Suprep®). The sponsor did not conduct any nonclinical study in support of the NDA. This NDA does not contain a nonclinical section (Module 4) or any nonclinical study report.
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

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
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
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?	√		The proposed labeling sections relevant to nonclinical studies may need to be revised during the labeling review.
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?			N/A
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 is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant. **None**

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. **None**

Tamal K. Chakrabortit, Ph.D. — August 27, 2012
Reviewing Pharmacologist — Date

Sushanta K. Chakder, Ph.D. — August 27, 2012
Supervisor — Date

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

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/s/

TAMAL K CHAKRABORTI
08/27/2012

SUSHANTA K CHAKDER
08/27/2012