CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203595Orig1s000

PHARMACOLOGY REVIEW(S)

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

FROM: David B. Joseph
Pharmacology Team Leader

DATE: October 11, 2012

SUBJECT: NDA 203,595 (SD # 1 received December 19, 2011)

Sponsor: Braintree Laboratories, Inc.

Drug Product: Suclear

Comments:

Nonclinical studies with Suclear were not conducted, nor did the Agency request such studies to support clinical testing or approval of this drug product, based on the following considerations:

1. Suclear is a combination of two approved drug products, including sulfate salts at one half the approved dose in SUPREP, and PEG 3350 + electrolytes at the approved dose in HalfLytely and Bisacodyl Tablet Bowel Prep Kit. The sulfate salts are supplied as a separate component to be taken first, followed by consumption of PEG 3350 + electrolytes in the second component.

2. Both components of Suclear have the same mechanism of action (i.e. osmotic effects within the colon leading to fluid movement into the lumen and catharsis).

3. Toxicity studies were previously conducted on the individual components of Suclear to support approval of other drug products indicated for bowel cleansing prior to colonoscopy, as cited in Dr. Ng's Pharmacology/Toxicology review of this application.

4. Suclear is a single-use product containing two approved osmotic agents that are administered separately. Therefore, the probability of new or unexpected toxicities resulting from this drug combination is minimal.

Recommendations:

There are no nonclinical issues which preclude the approval of Suclear. I concur with Dr. Ng's recommendation for approval, and his recommendations for labeling revisions.

_____ _____

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

cc:
NDA 203,595
DGIEP
DGIEP/PM
DGIEP/Dr. Joseph
DGIEP/Dr. Ng
DGIEP/Dr. Fiorentino

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/s/

DAVID B JOSEPH
10/11/2012

ADDENDUM TO PHARMACOLOGY/TOXICOLOGY REVIEW OF NDA 203,595 DATED SEPTEMBER 14, 2012

Reviewer: Yuk-Chow Ng, Ph.D.

Date: 10/03/2012

(b) (4) and (b) (4) are potential process impurities that may be present in polyethylene glycol 3350 (PEG), which is one of the drug substances contained in SuClear. The Sponsor justifies their initial proposed limit of (b) (4) for (b) (4) based on the recommendation in ICH guidance Q3C under (b) (4). However, this limit applies to drug products with a daily dose less than (b) (4) per day. Because the one day intake of PEG in the proposed dosing is 210 g, the Agency informed the Sponsor that the limit should be calculated based on the Permissible Daily Exposure (PDE) level stated in ICH Q3C, which is (b) (4) or (b) (4) based on an intake of 210 g PEG (teleconference on July 16, 2012). Because (b) (4) is considered to have similar toxicity as observed for (b) (4) the Agency requested the Sponsor to set a limit of (b) (4) for the combined total amount of (b) (4) and (b) (4)

In the correspondence dated September 10, 2012, the Sponsor indicated that they will be able to reduce the specified combined limit for (b) (4) and (b) (4) to (b) (4) The proposed specified limit is acceptable based on the following reasons:

1. The PDE of (b) (4) stated in ICH Q3C is intended as a limit for a lifetime exposure of (b) (4) Because SuClear is taken only as a one-time dose, the higher limit of (b) (4) proposed by the Sponsor is deemed reasonable for this drug product.

2. The Agency for Toxic Substances and Disease Registry (ATSDR) sets a MRL (Minimal Risk Level) of (b) (4) for (b) (4) in intermediate-duration exposure (15-364 days). This level is equivalent to (b) (4) at a 210 g PEG dose, based on a 60-kg bodyweight. Thus, the maximum (b) (4) dose (b) (4) in a 60-kg patient) at the newly proposed limit is well below the MRL.

3. The Environmental Protection Agency (EPA) has set the RD (Reference Dose) at (b) (4) for (b) (4) which is equivalent to (b) (4) in a 210 g PEG dose, based on a 60-kg bodyweight.

4. Although SuClear in indicated for use in adults only, the safety concern related to the potential presence of (b) (4) and (b) (4) is also relevant to pediatric

patients, given that clinical studies in pediatric patients will be required after approval of this application. Thus, the limit for combined (b) (4) and (b) (4) should provide a reasonable assurance of safety in both adult and pediatric patient populations. (b) (4)

The totality of the information described above provides a reasonable assurance of safety in both adult and pediatric patients, with respect to the newly proposed limit of (b) (4) for the combined amount of (b) (4) and (b) (4) in the PEG component of SuClear.

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 203,595
DGIEP
DGIEP/PM
DGIEP/Dr. Joseph
DGIEP/Dr. Ng
R/D Init.: D. Joseph 10/3/12

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/s/

YUK-CHOW NG
10/04/2012

DAVID B JOSEPH
10/04/2012
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:	203,595
Supporting document/s:	001
Applicant's letter date:	12/19/2011
CDER stamp date:	12/19/2011
Product:	SuClear®
Indication:	Cleansing of the colon in preparation for colonoscopy in adults
Applicant:	Braintree Laboratories Inc. Braintree, MA
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:	Matthew C. Scherer

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 203,595 are owned by Braintree Laboratories Inc. or are data for which Braintree Laboratories Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 203,595 that Braintree Laboratories 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 203,595.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

SuClear is a colonic cleansing agent intended as a preparation for colonoscopy in adults. The preparation consists of two component steps, an oral sulfate solution containing about 22 grams of sulfate salts (sodium sulfate, potassium sulfate and magnesium sulfate), followed by 2L of a polyethylene glycol and electrolytes solution (PEG-ELS). Both of these components are present in previously approved colon cleansing agents. The oral sulfate solution is included in Suprep® (NDA 22-372; sodium sulfate, potassium sulfate, and magnesium sulfate for oral solution), at twice the recommended dose in the current NDA. The PEG-ELS component of SuClear is identical in composition and dosage to that in HalfLytely (NDA 21-551). This PEG-ELS component also is identical in composition, but one half of the dose of the PEG-ELS component contained in NuLytely (NDA 19-797).

Both components of SuClear are osmotically active agents. Because they are poorly absorbed, the sulfate salts and PEG remain in the lumen of the gastrointestinal tract where they exert an osmotic effect. The osmotic activity of SuClear thus increases the water content of stool, and thereby causes a watery diarrhea, cleansing the colon in preparation for colonoscopy.

The Sponsor did not submit any new nonclinical studies to support the current application. All nonclinical toxicology studies on the SuClear components were submitted and reviewed previously under NDA 21-551 (HalfLytely), NDA 19-797 (NuLytely), NDA 22-372 (Suprep®), and NDA 22-015 (Miralax®). The review of nonclinical studies with Suprep, the sulfate salt component, concluded that the animal data adequately supported the proposed use at the intended therapeutic dosage (Pharmacology/Toxicology review of NDA 22-372 by Dr. Tamal Chakraborti, dated 03/06/2009). Regarding the PEG-ELS component of the agent, it was concluded that PEG-ELS did not produce any signs of toxicity, except soft stools and diarrhea, in dogs. In addition, the safety of the PEG-ELS components in HalfLytely is well established through its clinical and post-marketing experience (Pharmacology/Toxicology review of NDA 21-551 by Dr. Tamal Chakraborti, dated 11/13/2002). Therefore, from a nonclinical standpoint, there is no safety concern for the proposed use of SuClear.

1.2 Brief Discussion of Nonclinical Findings

No nonclinical studies were submitted. (b) (4) and (b) (4) are potential process impurities that may be present in polyethylene glycol 3350 (PEG), which is one of the drug substances contained in SuClear. The Sponsor justifies their proposed limit of (b) (4) for (b) (4) based on the recommendation in ICH Q3C under (b) (4). However, this limit applies to drug products with a daily dose less than (b) (4) per day. Because the one day intake of PEG in the

proposed dosing is 210 g, the limit should be calculated based on the ICH Permissible Daily Exposure (PDE) level, which is (b) (4) or (b) (4) based on an intake of 210 g PEG. (b) (4) is considered to have similar toxicity as observed for (b) (4), therefore the Sponsor should be asked to set a limit of (b) (4) for the combined total amount of (b) (4) and (b) (4)

1.3 Recommendations

1.3.1 Approvability

The application is recommended for approval.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

Sponsor's Proposed Version:

8.1 Pregnancy

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

Evaluation:

The description (b) (4) should be deleted.

Recommended Version:

8.1 Pregnancy

Pregnancy Category C

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

Sponsor's Proposed Version:

12.1 Mechanism of Action

The primary mode of action is the osmotic effect of the un-absorbed PEG and sulfate salts. Sulfate salts provide sulfate anions, which are poorly absorbed. The osmotic effect of unabsorbed sulfate anions and the associated cations cause water to be retained within the gastrointestinal tract. Polyethylene glycol (PEG) is also a largely unabsorbed osmotic agent which causes water to be retained within the gastrointestinal tract.

Evaluation:
In the third sentence, the word “cause” should be replaced by “causes”. The stated mechanism of action for SuClear is similar to that described for Suprep and HalfLytely, and is therefore acceptable, with exception of the single recommended change.

Sponsor’s Proposed Version:

12.3 Pharmacokinetics

(b) (4)

Evaluation:

The last sentence in this section contains (b) (4) that was not provided in this NDA. Furthermore, (b) (4) is generally inappropriate for this section. Therefore, the sentence should be deleted.

Recommended version:

12.3 Pharmacokinetics

(b) (4)

[redacted]

Sponsor's Proposed Version:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of SuClear. Studies to evaluate the possible impairment of fertility or mutagenic potential of SuClear have not been performed.

Evaluation:
Acceptable, no changes are needed.

Sponsor's Proposed Version:

13.2 Animal Toxicology and/or Pharmacology

The sulfate salts of sodium, potassium, and magnesium contained in SuClear were administered orally (gavage) to rats and dogs up to 28 days up to a maximum daily dose of 5 g/kg/day (approximately [redacted] and [redacted] times for rats and dogs, respectively, the recommended human dose of [redacted] or [redacted] 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.

(b) (4)

Evaluation:

Because the recommended human dose for the sulfate salts of sodium, potassium, and magnesium is 22 g/day, not (b) (4) as stated, the human dose multiples should be revised as below in the recommended version. Otherwise, the paragraph within this section is identical to the currently approved labeling for Suprep®, and is therefore acceptable.

The second paragraph in this section describes toxicity study findings regarding PEG 3350. This (b) (4) is not necessary to assure safe and effective use of SuClear in humans, and should therefore be deleted (21 CFR 201.57).

Recommended version:

13.2 Animal Toxicology and/or Pharmacology

The sulfate salts of sodium, potassium, and magnesium contained in SuClear were administered orally (gavage) to rats and dogs up to 28 days up to a maximum daily dose of 5 g/kg/day (approximately 1.8 and 6 times for rats and dogs, respectively, the recommended human dose of 22 g/day or 0.44 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.

2 Drug Information

2.1 Drug

Generic Names

Sodium Sulfate, Potassium Sulfate, and Magnesium Sulfate

Polyethylene Glycol (PEG)-3350, Sodium Chloride, Sodium Bicarbonate, Potassium Chloride

Code Name

BLI-850

Chemical Names

Same as generic names

Molecular Formula/Molecular Weight

Sodium sulfate: Na_2SO_4/142.04
Potassium sulfate: K_2SO_4/174.26
Magnesium sulfate: $MgSO_4$/120.37

Polyethylene glycol 3350: $H(OCH_2CH_2)nOH$/3350 (approximate)
Sodium chloride: NaCl/58.44
Sodium bicarbonate: $NaHCO_3$/84.01
Potassium chloride: KCl/74.55

Pharmacologic Class: Osmotic laxative

2.2 Relevant INDs, NDAs, and DMFs

1. IND 102,894 (BLI-850 Oral Sulfate (sodium, potassium, magnesium) Solution and PEG-ELS Kit)
2. NDA 22-372 (Suprep®, Braintree Laboratories, Inc.)
3. IND 57,673 (1/2 Lytely bowel prep (b) (4) Braintree Laboratories, Inc.)
4. NDA 21-551 (HalfLytely®, Braintree Laboratories, Inc.)
5. NDA 19-797 (NuLytely®, Braintree Laboratories, Inc.)

2.3 Drug Formulation

SuClear is supplied as a kit containing one 6 oz bottle of the liquid sulfate formulation and a 2L (b) (4) bottle containing the polyethylene glycol and salts. Using a supplied 16 oz cup, patients add water (to 16 oz) to the contents of the 6 oz bottle of sulfate and drink the resulting solution. Then patients reconstitute the PEG-ELS to 2L and consume the contents.

The sulfate salt component of SuClear contains the following active ingredients: sodium sulfate (17.5 g), potassium sulfate (3.13 g), and magnesium sulfate (1.6 g). The PEG-ELS component of SuClear contains the following active ingredients: Polyethylene

Glycol 3350 (210 g), sodium chloride (5.6 g), sodium bicarbonate (2.86 g), and potassium chloride (0.74 g)

The following table shows the excipients for the sulfate salt component of SuClear, which is identical to that of Suprep.

Raw Material and Grade Quality	Quantity per Dose (6 oz. bottle)	Function
Sodium Benzoate, NF		(b) (4)
Sucralose (b) (4) (b) (4)		
Malic Acid, FCC		
Citric Acid, USP		
(b) (4) Flavor (b) (4)		
Purified Water, USP		

The following table shows the excipients for the PEG-ELS component of SuClear, which is identical to that of HalfLytely.

Raw Material and Grade Quality	Quantity per Dose (2L bottle)	Function
(b) (4) Cherry Flavor	1.00 g	Flavoring agent
Lemon-Lime Flavor	1.00 g	Flavoring agent
Orange Flavor	1.00 g	Flavoring agent
Pineapple Flavor	1.00 g	Flavoring agent

2.4 Comments on Novel Excipients

There are no novel excipients. All the excipients are identical to that described in Suprep and HalfLytely.

2.5 Comments on Impurities/Degradants of Concern

(b) (4) and (b) (4) are potential process impurities that may be present in polyethylene glycol 3350 (PEG), which is one of the drug substances contained in SuClear. The Sponsor justifies their proposed limit of (b) (4) for (b) (4) based on the recommendation in ICH Q3C under (b) (4)

However, this limit applies to drug products with a daily dose less than (b) (4) per day. Because the one day intake of PEG in the proposed dosing is 210 g, the limits should be calculated based on the ICH Permissible Daily Exposure (PDE) level, which is (b) (4) or (b) (4) based on an intake of 210 g PEG. (b) (4) is considered to have similar toxicity as observed for (b) (4), therefore the Sponsor should be asked to set a limit of (b) (4) for the combined total of (b) (4) and (b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

SuClear is indicated for cleansing of the colon in preparation for colonoscopy in adults. SuClear is supplied as a kit containing one 6 oz bottle of the liquid sulfate formulation and a 2L (b) (4) bottle containing the polyethylene glycol and salts. Using a supplied 16 oz cup, patients add water (to 16 oz) to the contents of the 6 oz bottle of sulfate and drink the resulting solution. Patients reconstitute the PEG-ELS to 2L and consume the contents.

2.7 Regulatory Background

SuClear consists of two component steps which have been included in previously approved colon cleansing products marketed by Braintree, the Sponsor of the current NDA. The oral sulfate solution was described in NDA 22-372 (Suprep®), which contains twice the sulfate content of SuClear. The PEG-ELS component of SuClear is identical in composition and dosage to that given in the HalfLytely solution (NDA 21-551). In addition, the PEG-ELS component also is identical in composition, but one half of the dose of the PEG-ELS component contained in NuLytely (NDA 19-797). Clinical studies of SuClear were conducted under IND 102,894.

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

SuClear consists of two components from two approved drug products for colon cleansing, both of which are owned by Braintree. The oral sulfate solution was described in NDA 22-372 (Suprep), which contains twice the sulfate content of SuClear. The PEG-ELS component of SuClear is identical in composition and dosage to that given in the HalfLytely solution (NDA 21-551). Furthermore, the PEG-ELS component is identical in composition but one half of the volume of the PEG-ELS which is contained in NuLytely (NDA 19-797). SuClear is indicated for cleansing of the colon in preparation for colonoscopy in adults.

In the current NDA, the Sponsor did not submit any new nonclinical studies to support the application. All nonclinical toxicology studies relevant to the components of SuClear were submitted and reviewed previously under NDA 21-551, NDA 19-797, NDA 22-372, and NDA 22-015.

The sulfate salt component was reviewed under NDA 22-372. The following conclusions and recommendations regarding Suprep are taken from Dr. Tamal Chakraborti's review dated 03/06/2009:

"SuPrep® (BLI800) is a liquid concentrate for oral administration that comprises the following salts: sodium sulfate, potassium sulfate, and magnesium sulfate. Suprep is indicated for cleansing of the colon in preparation for colonoscopy. The pharmacodynamic action of Suprep relies on the retention of water in the intestines. The principal osmotic components of Suprep are magnesium and sulfate, with sulfate contributing the larger proportion of osmotic load. Both are poorly absorbed above a point of saturation, forcing water to remain in the intestines.

In this NDA, the sponsor has provided the following study reports: 7- (non-GLP, dose ranging studies) and 28-day oral toxicology studies in rats and dogs. The above studies were conducted as per the Division recommendations (Division meeting minutes dated April 20, 2007). The Division did not require any other studies to support the marketing approval of Suprep.

In a 28-day oral (gavage) toxicology study in rats, animals were treated with BLI800 at 1.25, 2.5 and 5.0 g/kg/day. BLI800 caused diarrhea. Treatment-related electrolyte and metabolic changes included hypochloremia, hypokalemia, hyponatremia and lower serum osmolality, higher urine sodium and potassium, alkaline urine and high serum bicarbonate indicative of metabolic alkalosis. BLI800 treatment decreased thymus weight at the high dose. The target organs could be the adrenal cortex (alteration of vacuolation), colon (dilated colon), jejunum (dilated) and kidney (minimal mineralization).

In a 28-day oral (gavage) toxicology study in Beagle dogs, animals were treated with BLI800 by oral gavage at 1.25, 2.5 and 5.0 g/kg/day. BLI800 caused emesis, excessive salivation, excessive drinking of water and abnormal excreta (soft and/or mucoid feces and/or diarrhea). BLI008 increased urine pH and sodium excretion. The target organ could not be identified in the absence of any significant organ toxicity.

The systemic toxicity of Suprep was adequately tested in rats and dogs as per the Division recommendations. Suprep was administered orally (gavage) to rats and dogs for up to 28 days up to a maximum daily dose of 5 g/kg/day (approximately 0.9 and 3 times, respectively, the recommended human dose of 44.48 g/day or 0.89 g/kg based on the body surface area). Suprep caused diarrhea, electrolyte and metabolic changes, including hypochloremia, hypokalemia, hyponatremia and lower serum osmolality, higher urine sodium and potassium, alkaline urine and high serum bicarbonate indicative of metabolic alkalosis. In dogs, Suprep 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. There appears to be no significant safety concern from a nonclinical standpoint for the proposed indication.

In conclusion, non-clinical studies conducted with Suprep appear to adequately support its proposed use at the intended therapeutic dosage and in accordance with the proposed product labeling."

The PEG-ELS component was reviewed under NDA 21-551. The following conclusions and recommendations regarding HalfLytely are taken from Dr. Tamal Chakraborti's review dated 11/13/2002.

"The sponsor did not conduct any preclinical toxicology study with HalfLytely. However, a 3-Day study with Vet-Prep (Polyethylene Glycol/Electrolyte Solutions or PEG-ELS for veterinary use of PEG-ELS) was included in this submission." "In addition, the sponsor cited literature references regarding the acute and chronic individual toxicity studies with polyethylene glycol (PEG) and bisacodyl."

"In a 3-Day study in beagle dogs with Vet-Prep, dogs were treated by oral gavage with PEG-ELS at 15.8 g/kg/day for 3 consecutive days. In this study, PEG-ELS did not produce any signs of toxicity except soft stools and diarrhea."

"The safety of the PEG and electrolyte components in HalfLytely is well established through its clinical and postmarketing experience. Therefore, from a preclinical standpoint, there is no safety concern for the proposed use of HalfLytely Bowel Prep (b) (4) This submission satisfies the criteria for marketing authorization of HalfLytely Bowel Prep (b) (4) and appears to be safe for the proposed use."

(b) (4) and (b) (4) are potential process impurities that may be present in the PEG drug substance in SuClear. The Sponsor justifies their proposed limit of (b) (4) for (b) (4) based on the recommendation in ICH Q3C under (b) (4) However, the limit applies to drug products with a daily dose less than (b) (4) per day. Because the one day intake of PEG in the proposed dosing is 210 g, the limit should be calculated based on the ICH Permissible Daily Exposure (PDE) level, which is (b) (4) or (b) (4) based on an intake of 210 g PEG. The toxicity of (b) (4) is considered to be similar to that of (b) (4). Therefore, the Sponsor should be asked to set a limit of (b) (4) for the combined total amount of (b) (4) and (b) (4)

In summary, SuClear consists of two components from the approved drug products, Suprep and HalfLytely, for use as colon cleansing agents. Based on the previous nonclinical studies conducted in support of Suprep and HalfLytely, and the clinical experience with these products, SuClear appears to be safe for the proposed use.

Recommendations:

From a nonclinical standpoint, this application should be approved.

Suggested labeling: The labeling should be changed as described in the "EXECUTIVE SUMMARY" section of this review.

cc:
ORIG NDA 203,595
DGIEP
DGIEP/PM
DGIEP/DR. JOSEPH
DGIEP/DR. NG
DGIEP/DR. LEE
DGIEP/DR. FIORENTINO
R/D INIT.: D. JOSEPH 8/31/12

12 Appendix/Attachments

None

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/s/

YUK-CHOW NG
09/13/2012
This application should be approved.

DAVID B JOSEPH
09/14/2012
I concur.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 203,595 **Applicant: Braintree Laboratories Inc** **Stamp Date: 12/19/2011**

Drug Name: (b) (4) **NDA/BLA Type: NDA**

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.

None.

Yuk-Chow Ng — February 2, 2012
Reviewing Pharmacologist — Date

David Joseph — February 2, 2012
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
02/01/2012
Fileable

DAVID B JOSEPH
02/02/2012