CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022372Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-372**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**7/2/08**
PRODUCT:	**Suprep® (Sodium sulfate, potassium sulfate, magnesium sulfate oral solution)**
INTENDED CLINICAL POPULATION:	**Indicated for cleansing of the colon in preparation for colonoscopy**
SPONSOR:	**Braintree Laboratories, Inc.**
DOCUMENTS REVIEWED:	**Nonclinical Study Reports**
REVIEW DIVISION:	**Division of Gastroenterology Products (DGP)**
PHARM/TOX REVIEWER:	**Tamal K. Chakraborti, Ph.D.**
PHARM/TOX SUPERVISOR:	**Sushanta K. Chakder, Ph.D.**
DIVISION DIRECTOR (ACTING):	**Donna Griebel, M.D.**
PROJECT MANAGER:	**Matthew C. Scherer, MBA**

Date of review submission to Division File System (DFS): March 6, 2009

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on Approvability: From a nonclinical perspective, this NDA may be approved.

B. Recommendation for Nonclinical studies: None

C. Recommendations on Labeling: The draft labeling of Suprep generally conforms to the format specified under 21CFR 201.56(d) and 201.57 for the content and format of labeling for human prescription drugs. However, the following changes should be incorporated.

8.1 Pregnancy

Sponsor's Version:

8.1 PREGNANCY

(b) (4)

Evaluation: The text is not in accordance with 21CFR 201.57(f)(6)(i)(c). The labeling should be modified as proposed below.

Proposed Version:

"8.1 Pregnancy

Teratogenic effects. Pregnancy category C.

Animal reproduction studies have not been conducted with SuPrep. (b) (4)

8.3. Nursing Mothers

Sponsor'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 SuPrep Bowel Prep Kit is administered to a nursing woman.

Evaluation: The text is not in accordance with 21CFR 201.57(f)(8)(iii) and acceptable. However, the text should be modified as proposed below.

Proposed Version:

"8.3 NURSING MOTHERS

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

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Sponsor's Version:

13.1 CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

(b) (4)

Evaluation: The text is in accordance with 21CFR 201.57(f)(5). However, the labeling should be modified as proposed below.

Proposed Version:

"13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of Suprep Bowel Prep Kit. Studies to evaluate the possible impairment of fertility or mutagenic potential of Suprep Bowel Prep Kit have not been performed."

13.2 Animal toxicology and/or pharmacology

Sponsor's Version:

(b) (4)

Evaluation: The text should be modified to focus findings with Suprep only and the text should contain the findings of the animal toxicology studies. The text should be modified as proposed below.

Recommended Version:

"13.2 Animal toxicology and/or pharmacology

The sulfate salts of sodium, potassium and magnesium contained in SuPrep Bowel Prep Kit 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, respectively, the recommended human dose of 44.48 g/day or 0.89 g/kg based on the body surface area). (b) (4) caused diarrhea, electrolyte and metabolic changes, including hypochloremia, hypokalemia, hyponatremia and lower serum osmolality, (b) (4) and high serum bicarbonate (b) (4). In dogs, (b) (4) 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."

II. Summary of nonclinical findings

A. Brief Overview of Nonclinical Findings: The systemic toxicity of Suprep was tested in rats and dogs following up to 28 days of oral administration as per the Division recommendations (Division meeting minutes dated April 20, 2007).

The sulfate salts of sodium, potassium and magnesium contained in SuPrep Bowel Prep Kit were administered orally (gavage) to rats and dogs for as long as 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. In rats, the target organs appeared to be the adrenal cortex (alteration of vacuolation), colon (dilated colon), jejunum (dilated) and kidney

(minimal mineralization). In dogs, no significant organ toxicities were observed.

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.

Pharmacologic Activity: The pharmacodynamic action of BLI800 relies on the retention of water in the intestines. The principal osmotic components of BLI800 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. No formal non-clinical pharmacodynamic (PD) studies were conducted as part of this NDA.

B. Nonclinical Safety Issues Relevant to Clinical Use: Suprep caused electrolyte and metabolic changes in animals such as hypochloremia, hypokalemia, hyponatremia and lower serum osmolality, higher urine sodium and potassium, alkaline urine and high serum bicarbonate indicative of metabolic alkalosis.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-372
Review number: 000
Sequence number/date/type of submission: 000/July 1, 2008/Original
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Braintree Laboratories, Inc., Braintree, MA
Manufacturer for drug substance:

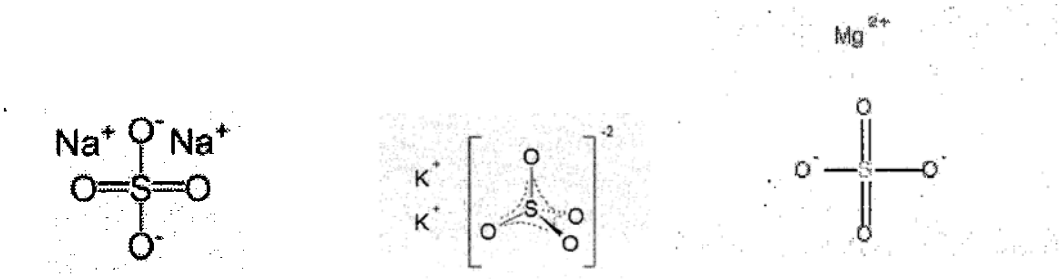
Sodium Sulfate: (b) (4)
Potassium Sulfate: (b) (4)
Magnesium Sulfate: (b) (4)

Reviewer name: Tamal. K. Chakraborti
Division name: Division of Gastroenterology Products (DGP)
Review completion date: March 6, 2009

Drug:

Trade name: Suprep
Generic name: Sodium sulfate, potassium sulfate, magnesium sulfate
Code name: BLI800
Chemical name: Sodium sulfate, potassium sulfate, magnesium sulfate
CAS registry numbers:
Sodium sulfate: 7757-82-6
Potassium sulfate: 7778-80-5
Magnesium sulfate: 7487-88-9
Molecular formula/molecular weight:
Sodium sulfate: Na_2SO_4/142.04
Potassium sulfate: K_2SO_4/174.26
Magnesium sulfate: $MgSO_4$/120.37

Structure:



Relevant INDs/NDAs/DMFs: None

Drug class: Bowel cleansing agent

Intended clinical population: Suprep is indicated for cleansing of the colon in preparation for colonoscopy.

Clinical formulation: The drug product, SuPrep (sodium sulfate, potassium sulfate and magnesium sulfate for oral solution) is a liquid concentrate for oral administration that is comprised of the following salts: sodium sulfate, USP, potassium sulfate, FCC and magnesium sulfate, USP. The drug product is packaged in two, 6 oz (b) (4) bottles with a child resistant closure. The following Table (from page 23 of Mod. 2, V 1.1) shows the composition.

Table 1. Drug Product Composition

Raw Material and Grade Quality	Quantity per 6 oz bottle	Quantity per Dose (2-6 oz bottles)	Function
Sodium Sulfate, USP	17.510 g	35.020 g	Active ingredient
Potassium Sulfate, FCC	3.130 g	6.260 g	Active ingredient
Magnesium Sulfate Anhydrous, USP	1.600 g	3.200 g	Active ingredient
Sodium Benzoate, NF	(b) (4)		
Sucralose (b) (4)			
Malic Acid, FCC			
Citric Acid, USP			
(b) (4)			
Purified Water, USP			

Route of administration: Oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission: The following table lists the studies reviewed in this submission.

STUDY	REPORT NO.	TESTING LAB.	VOLUME NO.	REV. PAGE #
TOXICOLOGY				
Rat				
28-Day, PO	382037	(b) (4)	Mod.. 4; 3.1	12
Dog				
28-Day, PO	382039	(b) (4)	Mod. 4, 5.1	25

Studies not reviewed within this submission: Method validation study report ((b) (4) 382034) was not reviewed.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

The sponsor did not conduct any pharmacology studies with Suprep. The pharmacodynamic action of BLI800 relies on the retention of water in the intestines. The principal osmotic components of BLI800 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.

2.6.2.2 Primary pharmacodynamics

None

2.6.2.3 Secondary pharmacodynamics

None

2.6.2.4 Safety pharmacology

None

2.6.2.5 Pharmacodynamic drug interactions

None

2.6.3 PHARMACOLOGY TABULATED SUMMARY

None included

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

The sponsor did not conduct any ADME studies with Suprep. The sponsor cited literature regarding pharmacokinetics of sulfate, which is discussed below. Morris and Levy (Morris ME and Levy G. Clin Pharmacol Ther. 1983; 33:529-36) reported that serum levels rose from a baseline of 410 µM to 510 µM two hours after an oral dose of 9.0 g of sodium sulfate. When magnesium sulfate was given intravenously as a preventive for eclampsia, serum levels rose from 850 to 1550 µM (Ricci J et al., Am J Nephrol. 1990; 10:409-11). The main route of elimination was *via* the urine, with estimates that 60-80% of the dose was eliminated by that route (Abernathy CO et al., Crt Rev Clin Lab Sci. 2000; 37:401-5). The absorption of sulfate from its magnesium salt appeared to be less than other salts; only about 30% was detected in the urine in 24 hours after an oral dose of 13.9 g (Morris ME and Levy G. Clin Pharmacol Ther. 1983; 33:529-36).

2.6.4.2 Methods of Analysis

None

2.6.4.3 Absorption

None

2.6.4.4 Distribution

None

2.6.4.5 Metabolism

None

2.6.4.6 Excretion

None

2.6.4.7 Pharmacokinetic drug interactions

None

2.6.4.8 Other Pharmacokinetic Studies

None

2.6.4.9 Discussion and Conclusions

Both magnesium and sulfates are poorly absorbed from the intestine. The main route of elimination of sulfate was reported to be *via* the urine, with estimates that 60-80% of the dose was eliminated through urine. The absorption of sulfate from its magnesium salt reported to be less than other salts.

2.6.4.10 Tables and figures to include comparative TK summary

None included

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

None included

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General Toxicology: In rats, the oral LD_{50} for sodium sulfate is 3 to 4 g/kg and the intraperitoneal LD_{50} is more than 3 g/kg.

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, electrolyte and metabolic changes, including hypochloremia, hypokalemia, hyponatremia and lower serum osmolality in female rats, higher urine sodium and potassium, alkaline urine and high serum bicarbonate indicative of metabolic alkalosis. BLI800 decreased thymus weight at the high dose. The target organ in rats appeared to 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.

Genetic Toxicology: None

Carcinogenicity: None

Reproductive Toxicology: None

Special Toxicology: None

2.6.6.2 Single-dose toxicity

None

2.6.6.3 Repeat-dose toxicity

Study Title: 28-Day Oral Toxicology Study in Rats

Key study findings: In a 28-day oral toxicology study in rats, animals were treated with BLI800 (combination of sodium sulfate, potassium sulfate and magnesium sulfate) by oral gavage at 1.25, 2.5 and 5.0 g/kg/day. The following are the key study findings.

- Rats treated with BLI800 developed 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 decreased thymus weight at the high dose
- Histopathological changes were observed in the adrenal cortex (alteration of vacuolation), colon (dilated colon), jejunum (dilated) and kidney (minimal mineralization).
- Administration of Oral Sodium Phosphate (OSP) at 5.13 g/kg/day caused mortality (probably due to renal insufficiency) and organ toxicity including renal tubular degeneration and mineral deposition (most likely calcium phosphate) in the kidneys, mineralization in the stomach and aorta and cardiac and hepatic degeneration and necrosis.

Study no.: (b) (4)-382037
Volume #, and page #: Module 4, Vol. 3.1-3.3, 1
Conducting laboratory and location: (b) (4)
Date of study initiation: May 29, 2007
GLP compliance: A statement of compliance was included
QA report: yes (X) no ( )
Drug, lot #, and % purity: BLI800 (Sodium sulfate, potassium sulfate and magnesium sulfate). The following table (page 21 of the study report) shows the batch numbers. The purity data for sodium sulfate, potassium sulfate and magnesium sulfate were 99.1-99.22%, 99.8% and 99.7%, respectively.

4.1.1. TEST ARTICLE 1 IDENTIFICATION

The test article, BLI800 (Oral Sulfate Solution [OSS]), is composed of 3 salts; sodium sulfate, potassium sulfate and magnesium sulfate. The 3 salts were received from Braintree Laboratories, Inc., Randolph, Massachusetts, as follows:

Identification	Quantity Received	Physical Description	Date of Receipt
Sodium Sulfate Lot no. C16X01 BRA no. 4936 [(b) (4) log no. 7474A]	(b) (4)	Fine, white powder	15 May 2007
Sodium Sulfate Lot no. C17X01 BRA no. 5074 [(b) (4) log no. 7474B]		Fine, white powder	27 June 2007
Potassium Sulfate Lot no. B25N24 BRA no. 3592 [(b) (4) log no. 7473A]		Fine, white powder	15 May 2007
Magnesium Sulfate Lot no. B39142 BRA no. 3780 [(b) (4) log no. 7475A]		Fine, white powder	15 May 2007

Methods:

Doses: 1.25, 2.5 and 5 g/kg/day

Basis of Dose Selection: The doses were selected based on the results of a 7-day non-GLP dose range-finding study in rats (Study No. 382036). In the dose ranging study, animals (n = 3/sex/dose) were treated with BLI800 (5 g/kg/day, Group 2, OSS) and Fleet Phospho Soda (5.13 g/kg/day, Group 3, OSP) or vehicle (Group 1) orally by gavage once daily for a minimum of 7 consecutive days. The dosage volume was 15 mL/kg for Groups 1 and 2, and 10 mL/kg for Group 3. There was no mortality. Clinical signs included swollen abdominal area, abnormal excreta (soft feces and/or diarrhea and yellow and/or brown material on various body surfaces (ventral trunk, hindlimbs, urogenital areas, and/or anogenita1 areas) at 5.0 g/kg/day (BLI800) and at 5.13 g/kg/day (OSP). Macroscopic observations of pale and/or enlarged kidneys, as well as histopathologic findings of mineral deposition in the kidney, were noted at 5.13 g/kg/day OSP group. There were no renal abnormalities (macroscopic or microscopic) in the vehicle or 5.0 g/kg/day (OSS). Based on the above, the doses

for the current study were chosen to demonstrate a graded toxic effect. It was anticipated that the high dose level of BLI800 would show drug-specific effects without producing a high incidence of fatalities. Dose levels of 1.25 and 2.5 g/kg/day were selected to be narrow enough to reveal any dose-related trends. The highest dose of 5 g/kg/day was the maximum feasible dose (MFD) based on solubility of the salts in water.

Species/strain: Sprague Dawley (SD) rats
Number/sex/group or time point (main study): 10/sex/group
Route, formulation and dose volume: Oral (gavage), solution in water, 15 mL/kg
Satellite groups used for toxicokinetics or recovery: None
Age: Approximately 7 to 8 weeks old
Weight: Males: 231-273 g; Females: 151-198 g
Study design: BLI800 (Oral Sulfate Solution or OSS) in the vehicle, deionized water, was administered orally by gavage once daily for 28 consecutive days to 3 groups (Groups 2 through 4). Fleet Phospho Soda (Oral Sodium Phosphate or OSP) was administered as a positive control (Group 5). BLI800 dosage levels were 1.25, 2.5 and 5.0 g/kg/day. The Fleet Phospho Soda dosage level was 5.13 g/kg/day. The following table (from page 25 of the study report) shows the study design.

Group Number	Test Article	Dosage Level (g/kg/day)[a]	Dosage Volume (mL/kg)	Number of Animals[b] Males	Females
1	Vehicle	0	15	10	10
2	BLI800	1.25	15	10	10
3	BLI800	2.5	15	10	10
4	BLI800	5.0	15	10	10
5	OSP	5.13	15	10	10

[a] = The dosing formulations were not adjusted for purity.
[b] = All surviving animals were euthanized following a minimum of 28 days of dose administration.

Observations and times:

Mortality: Mortality was observed twice daily.

Clinical signs: Clinical signs were observed three times daily.

Body weights: Body weight was recorded on a weekly basis.

Food consumption: Food consumption was recorded on a weekly basis.

Ophthalmoscopy: Ophthalmoscopic examinations were conducted at pretest and during Week 3 and 4.

Hematology: Hematology was conducted at necropsy.

Clinical chemistry: Clinical chemistry was conducted at necropsy.

Urinalysis: Urinalysis was conducted at necropsy.

Gross pathology: Gross pathology was conducted at necropsy.

Organ weights: The following (from page 34 of the study report) organs were weighed from all animals.

Adrenals	Pituitary
Brain	Prostate with seminal vesicles
Epididymides	Spleen
Heart	Testes
Kidneys	Thymus
Liver	Thyroid with parathyroids*
Ovaries with oviducts	Uterus

Histopathology: The following (from page 34 of the study report) organs/tissues from all animals were examined histopathologically.

Adrenals (2)
Aorta
Bone with marrow
  Femur with articular surface
  Sternum
Bone marrow smear (from femur)[a]
Brain
  Cerebrum 2 levels
  Cerebellum with medulla/pons
Cervix
Epididymides (2) [b]
Exorbital lacrimal gland (2)
Eyes with optic nerve (2) [c]
Gastrointestinal tract
  Esophagus
  Stomach
  Duodenum
  Jejunum
  Ileum
  Cecum*
  Colon*
  Rectum*
Harderian glands (2)
Heart
Kidneys (2)*
Liver (sections of 2 lobes)
Lungs (including bronchi, fixed by inflation with fixative)
Lymph node
  Mandibular
  Mesenteric
Ovaries with oviducts (2)[d]
Pancreas
Peripheral nerve (sciatic)
Pituitary
Prostate
Salivary glands [mandibular (2)]
Seminal vesicles (2)
Skeletal muscle (rectus femoris)
Skin (with mammary gland)[e]
Spinal cord (cervical, midthoracic, lumbar)
Spleen
Testes (2) [b]
Thymus
Thyroid [with parathyroids, (2)][d]
Tongue
Trachea
Urinary bladder
Uterus
Vagina
Gross lesions (when possible)*

Toxicokinetics: None

Results:

Mortality: All animals administered BLI800 at 1.25, 2.5 and 5.0 g/kg/day (Groups 2, 3 and 4, respectively) survived to the scheduled necropsy. The following (from page 37 of the study report) animals from the 5.13 g/kg/day OSP group (Group 5) were either found dead or euthanized in extremis prior to the scheduled necropsy.

Text Table 1. Fatalities Prior To Scheduled Necropsy In The 5.13 g/kg/day OSP Group

Date	Study Day[a]	Animal Number	Sex	Disposition
(b) (4)	6	67990	M	Found Dead
	9	68025	F	Euthanized In Extremis
	10	68009	F	Found Dead
	12	67987	M	Euthanized In Extremis
	12	67989	M	Euthanized In Extremis
	11	68040	F	Found Dead
	12	68060	F	Euthanized In Extremis
	14	67966	M	Euthanized In Extremis
	15	68046	F	Found Dead
	17	68039	F	Euthanized In Extremis
	19	67949	M	Euthanized In Extremis
	18	68056	F	Found Dead
	21	67957	M	Found Dead
	24	67954	M	Found Dead
	25	67965	M	Found Dead

a = Initiation of dosing (study day 0) was 14 June 2007 for males and 15 June 2007 for females.

Clinical signs of the above animals prior to euthanasia or the unscheduled deaths for animals in the 5.13 g/kg/day OSP group included body and/or extremities cool to touch, dermal atonia, hypo activity, impaired equilibrium, intermittent tremors, respiration decreased and/or labored, partial closure of right and/or left eyes, prostrate, and/or thin. The deaths were generally attributed to renal insufficiency.

Clinical signs: Test article-related clinical findings consisted of swollen abdominal area and/or abnormal excreta (soft feces and/or diarrhea, feces smaller than normal, and yellow and/ or brown material on urogenital and/or anogenital areas). Swollen abdominal area was first observed at approximately 4 hours post-dosing on study Day 7 at 5.0 g/kg/day, while abnormal excreta was first noted at 4 hours post-dosing on study Day 0 and was observed consistent1y throughout the study with the highest frequency occurring at 5.0 g/kg/day. The summary of clinical findings of diarrhea and soft feces is presented in the following text Table (from page 38 of the study report).

Text Table 2. Summary Of Number Of Occurrences Of Selected Clinical Observations[a]

	Males					Females				
Test Article	OSS				OSP	OSS				OSP
Dose Level (g/kg/dose)	0	1.25	2.5	5.0	5.13	0	1.25	2.5	5.0	5.13
Soft Feces	0	10	30	78	30	0	15	36	42	11
Diarrhea	0	1	21	54	10	0	1	20	48	11

a - Clinical observations for detailed physical examinations, at the time of dosing and 1 and 4 hours post-dosing.

Body weights: The mean initial (Week-3) and final (Week 4) body weights of control males were 136 and 394 g, respectively. The mean initial (Week-3) and final (Week 4) weight of control females were 110 and 244 g, respectively. In males, the mean body weights at Week 4 were 93.9%, 97.5% and 94.2% of control at 1.25, 2.5 and 5.0 g/kg/day, respectively. In females, the mean body weights at Week 4 were 98.4%, 99.6% and 100.4% of control at 1.25, 2.5 and 5.0 g/kg/day, respectively.

Food consumption: The mean initial (Week -1 to -2) and final (Week 3 to 4) food consumption in control males were 24 and 28 g/animal/day, respectively. The mean initial (Week -1 to -2) and final (Week 3 to 4) food consumption in control females were 19 and 20 g/animal/day, respectively. There were no significant treatment-related effects.

Ophthalmoscopy: There were no significant treatment-related ocular findings.

Hematology: No significant treatment-related changes were observed.

Clinical chemistry: Treatment-related serum chemistry changes included hypochloremia, hypokalemia, hyponatremia, increase in bicarbonate level indicating metabolic alkalosis, etc. The following Table (from page 43 of the study report) shows the serum chemistry changes.

Text Table 3. Serum Chemistry Alterations For Electrolyte And Bicarbonate Values (Study Day 28 Scheduled Necropsy)

	Males					Females				
	BLI800				OSP	BLI800				OSP
Dosage (g/kg/day):	0	1.25	2.5	5.0	5.13	0	1.25	2.5	5.0	5.13
Chloride	103	100**	97**	95**	96	103	100**	97**	94**	94**
Potassium[d]	4.7	4.5	4.0**	3.6**	3.7[a]	4.4	4.3	3.9**	3.6**	3.5**
Sodium	144	144	143	142	147	144	143	141**	140**	142
Bicarbonate	25	26	29**	30**	24	21	22	23	24	27**
Calcium	11.1	11.1	11.2	11.3	7.2[b]	11.1	11.0	10.9	11.1	9.9**
Phosphorus	8.5	8.8	8.1	8.1	23.5[c]	7.5	7.6	7.2	7.8	8.9*[e]
Calc. serum osmolality[d]	300.4	298.8	297.2	297.3	310.6	300.6	291.6**	295.2**	292.3**	296.1

[a] = Value similar to the 5.0 g/kg/day BLI800 group males and females and the 5.13 g/kg/day OSP group females; therefore, considered to be related to OSP administration. No statistical analysis conducted (n=2).
[b] = Value lower than the 5.13 g/kg/day OSP group females and lower than historical reference range values; therefore, considered related to OSP administration. No statistical analysis conducted (n=2).
[c] = Value considerably higher than the 5.13 g/kg/day OSP group females and higher than historical reference range values; therefore, considered to be related to OSP administration. No statistical analysis conducted (n=2).
[d] = Rounded values shown here represent values on Tables 17 and 18.
[e] = Falls within the range of (b) (4) Historical Control Data.
* = Significantly different from control group at $p < 0.05$ using Dunnett's test.
** = Significantly different from control group at $p < 0.01$ using Dunnett's test.

In addition, serum globulin was significantly lower at 5.0 g/kg/day in males and females, and at 5.13 g/kg/day OSP group males and females. The 5.0 g/kg/day BLI800 group and the 5.13 g/g/day OSP group males and females had significantly lower serum total protein. The serum urea nitrogen was 89% higher in the 5.13 g/kg/day OSP group males compared to control, and there was corresponding increase in the creatinine levels (250% higher). There was no BLI800-related alterations in the creatinine values as shown in the following Table (from page 44 of the study report).

Text Table 4. Serum Urea Nitrogen And Creatinine Value Alterations In Rats Administered 5.13 g/kg/day OSP (Study Day 28 Scheduled Necropsy)

	Males					Females				
	BLI800				OSP	BLI800				OSP
Dosage (g/kg/day):	0	1.25	2.5	5.0	5.13	0	1.25	2.5	5.0	5.13
Urea Nitrogen	16.6	16.8	15.4	18.4	31.4	19.6	20.1	20.0	16.9	19.6
Creatinine	0.2	0.2	0.1	0.1	0.7	0.3	0.3	0.2	0.2	0.3

Urinalysis: Sodium, potassium and pH were increased at almost all doses. In addition, there were treatment-related increased sodium and potassium clearance. The treatment-

related alterations in the urinalysis parameters are shown in the following Table (from page 45 of the study report).

Text Table 5. Urine Chemistry Alterations (Study Day 28 Scheduled Necropsy)

	Males					Females				
	BLI800				OSP	BLI800				OSP
Dosage (g/kg/day):	0	1.25	2.5	5.0	5.13	0	1.25	2.5	5.0	5.13
Urine Sodium	27	201**	409**	390**	289[a]	55	218**	370**	398**	301**
Urine Potassium	105	128	175*	129	53	110	166	186*	183*	78
Urine pH	6.8	6.1	6.9	8.0**	6.3	6.6	6.2	6.5	7.9**	6.5

[a] = Value similar to the 5.13 g/kg/day OSP group females and higher than the 1.25 g/kg/day BLI800 group males and females; therefore, considered to be related to OSP administration. No statistical analysis conducted (n=2).
* = Significantly different from control group at $p < 0.05$ using Dunnett's test.
** = Significantly different from control group at $p < 0.01$ using Dunnett's test.

No BLI800 related alterations were observed in the creatinine clearance rate with the exception of female rats at 5.0 g/kg/day, which showed low creatinine clearance rate. Renal function values are shown in the following table (from page 46 of the stuffy report).

Text Table 6. Renal Function Values (Study Day 28, Scheduled Necropsy)

	Males					Females				
	BLI800				OSP	BLI800				OSP
Dosage (g/kg/day):	0	1.25	2.5	5.0	5.13	0	1.25	2.5	5.0	5.13
Creatinine Clearance Rate	14.8	13.7	10.29	11.6	2.27	6.67	7.03	6.45	3.19**	4.51
Sodium Clearance Rate	0.005	0.030	0.060**	0.136**	0.178	0.01	0.031	0.072**	0.090**	0.115**
Fractional Excretion of Sodium	0.04	0.25	0.64**	1.56**	7.61	0.16	0.47	1.24**	2.80**	2.52**
Potassium Clearance Rate	0.61	0.64	0.94	1.79**	1.22 [a]	0.66	0.77	1.33*	1.48**	1.26

[a] = Value similar to the 5.13 g/kg/day OSP group females and higher than the 1.25 g/kg/day BLI800 group males and females; therefore, considered to be related to OSP administration. No statistical analysis conducted (n=2).
* = Significantly different from control group at $p < 0.05$ using Dunnett's test.
** = Significantly different from control group at $p < 0.01$ using Dunnett's test.

The urine creatinine values were 3-fold lower (approximately 66%) in male and female rats administered 5.0 g/kg/day BLI800 and similarly lower in male (approximately 78%)

and female rats (approximately 66%) administered 5.13 g/kg/day OSP. Rats administered 2.5 g/kg/day BLI800 also showed a trend toward lower urine creatinine values (approximately 20% lower) as shown in the following Table (from page 48 of the study report).

Text Table 7. Urine Creatinine Values (Study Day 28, Scheduled Necropsy)

	Males					Females				
	BLI800				OSP	BLI800				OSP
Dosage (g/kg/day):	0	1.25	2.5	5.0	5.13	0	1.25	2.5	5.0	5.13
Urine Creatinine [a]	75.7	83.7	59.0	25.6**	16.9 [a]	65.3	89.4	53.2	23.4**	22.3*

[a] = Values shown for 5.13 g/kg/day OSP group males was lower than 5.0 g/kg/day BLI800 group males. No statistical analysis was conducted (n=2).
* = Significantly different from control group at $p < 0.05$ using Dunnett's test.
** = Significantly different from control group at $p < 0.01$ using Dunnett's test.

Gross pathology: There were no treatment-related macroscopic observations.

Organ weights: The absolute and relative (to brain and final body weight) mean thymus weights were lower (significant for the males only) in the 5.0 g/kg/day BLI800 group. The absolute and relative (to brain and final body weight) mean thymus weights were lower in the animals in 5.13 g/kg/day OSP group. The results are shown in the following Table (from page 51 of the study report).

Text Table 9. Alterations In Organ Weight Associated With Administration Of 5.0 g/kg/day BLI800 and 5.13 g/kg/day OSP.

Parameter	Direction and magnitude of change (percent difference from control)	Dosage level (g/kg/day)	Sex
Thymus			
Absolute	↓26.4**	5.0	M
Relative to body weight	↓21.9*		
Relative to brain weight	↓22.7*		
Thymus			
Absolute	↓14.4	5.0	F
Relative to body weight	↓15.7		
Relative to brain weight	↓14.0		
Thymus			
Absolute	↓37.2	5.13	M
Relative to body weight	↓22.7		
Relative to brain weight	↓31.9		
Thymus			
Absolute	↓25.5	5.13	F
Relative to body weight	↓25.7		
Relative to brain weight	↓26.7		

* = significantly different from control group at $p < 0.05$ using Dunnett's test.
** = significantly different from control group at $p < 0.01$ using Dunnett's test.

Histopathology:

BLI800: BLI800-related microscopic findings included alteration of vacuolation in the adrenal cortex in the 1.25 and 2.5 g/kg/day males and the 5.0 g/kg/day male and female groups. Dilated colon was noted in a dose-related manner in the 1.25, 2.5 and the 5.0 g/kg/day males and females, with the highest incidence occurring at the highest dose. In addition, dilated jejunum was noted in a dose-related manner in the 1.25, 2.5 and 5.0 g/kg/day males. BLI800 also caused minimal mineralization of the kidney in females at mid- and high-dose. The histopathological changes are shown in the following Table (from page 53 of the study report).

Text Table 10. Incidence Of Selected Histopathologic Findings, Study Day 28 Scheduled Necropsy[a]

	Males					Females				
	BLI800				OSP	BLI800				OSP
Dosage (g/kg/day):	**0**	**1.25**	**2.5**	**5.0**	**5.13**	**0**	**1.25**	**2.5**	**5.0**	**5.13**
Adrenal Cortex[b]	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Vacuolation, cortex	0	2	5	6	4	0	0	0	6	2
Minimal	0	2	4	3	3	0	0	0	3	1
Mild	0	0	1	3	1	0	0	0	3	1
Colon[b]	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Dilatation, lumen	1	4	4	7	3	1	3	5	6	5
Present	1	4	4	7	3	1	3	5	6	5
Jejunum[b]	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Dilatation, lumen	0	2	4	6	3	0	0	1	0	1
Present	0	2	4	6	3	0	0	1	0	1

[a] = Incidences for the 5.13 g/kg/day OSP group (Group 5) includes animals found dead, euthanized in extremis and euthanized at the scheduled necropsy.

[b] = Number of tissues examined from each group.

OSP: Histopathological changes at 5.13 g/kg/day included renal tubular degeneration and mineralization. Mineral deposition also occurred in the mucosa of the glandular stomach, myocardium of the heart and in the aorta. The following Table (from page 54 of the study report) shows the histopathological changes.

Text Table 11. Incidence Of Selected Histopathologic Findings, Study Day 28 Scheduled Necropsy[a]

	Males					Females				
	BLI800				OSP	BLI800				OSP
Dosage (g/kg/day):	**0**	**1.25**	**2.5**	**5.0**	**5.13**	**0**	**1.25**	**2.5**	**5.0**	**5.13**
Kidney[b]	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Degeneration, tubular	0	0	0	0	10	0	0	0	0	10
Severe	0	0	0	0	2	0	0	0	0	4
Moderate	0	0	0	0	8	0	0	0	0	5
Mild	0	0	0	0	0	0	0	0	0	1
Mineralization	0	0	0	0	10	1[c]	0	1[c]	1[c]	10
Severe	0	0	0	0	5	0	0	0	0	4
Moderate	0	0	0	0	5	0	0	0	0	5
Mild	0	0	0	0	0	1[c]	0	0	0	1
Minimal	0	0	0	0	0	0	0	1[c]	1[c]	0
Stomach[b]	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Mineralization	0	0	0	0	8	0	0	0	0	8
Severe	0	0	0	0	0	0	0	0	0	1
Moderate	0	0	0	0	5	0	0	0	0	5
Mild	0	0	0	0	2	0	0	0	0	2
Minimal	0	0	0	0	1	0	0	0	0	0
Heart[b]	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Degeneration, myocardial	0	0	0	0	7	0	0	0	0	9
Severe	0	0	0	0	0	0	0	0	0	2
Moderate	0	0	0	0	4	0	0	0	0	1
Mild	0	0	0	0	2	0	0	0	0	2
Minimal	0	0	0	0	1	0	0	0	0	4
Aorta[b]	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Mineralization	0	0	0	0	2	0	0	0	0	1
Moderate	0	0	0	0	1	0	0	0	0	1
Mild	0	0	0	0	1	0	0	0	0	0

[a] = Incidences for the 5.13 g/kg/day OSP group (Group 5) includes animals found dead, euthanized in extremis and euthanized at the scheduled necropsy.

[b] = Number of tissues examined from each group.

[c] = Background level of mineralization with no test article significance.

Summary: In a 28-day oral toxicology study in rats, animals were treated with BLI800 (combination of sodium sulfate, potassium sulfate and magnesium sulfate) by oral gavage at 1.25, 2.5 and 5.0 g/kg/day. Rats treated with BLI800 developed 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. The target organs appeared to be the adrenal cortex (alteration of vacuolation), colon (dilated colon), jejunum (dilated) and urinary system (electrolyte imbalance). Administration of Oral Sodium Phosphate (OSP) at 5.13 g/kg/day caused mortality (probably due to renal insufficiency) and organ toxicity including renal tubular degeneration and mineral deposition (most likely calcium phosphate) in the kidneys, mineralization in the stomach and aorta and cardiac and hepatic degeneration and necrosis.

Study Title: 28-Day Oral Toxicology Study in Dogs

Key study findings: In a 28-day oral toxicology study in Beagle dogs, animals were treated with BLI800 (combination of sodium sulfate, potassium sulfate and magnesium sulfate) by oral gavage at 1.25, 2.5 and 5.0 g/kg/day. The following are the key study findings.

- Test article-related clinical findings consisted of emesis (containing food and/or white, yellow and/or clear material), wet clear material around mouth, excessive salivation, white frothy material around the mouth, excessive drinking of water and abnormal excreta (soft and/or mucoid feces and/or diarrhea). These findings were noted at all doses, with the highest incidence for most of the findings being noted at 5.0 g/kg/day.
- BLI008 increased urine pH and sodium excretion.
- The target organ could not be identified in the absence of any significant organ toxicity.

Study no.: (b) (4)-382039
Volume #, and page #: Module 4, Vol. 5.1-5.2
Conducting laboratory and location: (b) (4)
Date of study initiation: July 2, 2007
GLP compliance: A statement of compliance was included
QA report: yes (X) no ( )
Drug, lot #, and % purity: BLI800 (Sodium sulfate, potassium sulfate and magnesium sulfate). The following table (page 17 of the study report) shows the batch numbers. The purity data for sodium sulfate, potassium sulfate and magnesium sulfate were 99.1%, 99.8% and 100.3%, respectively.

Identification	Quantity Received	Physical Description
Sodium Sulfate Lot no. C17X01 BRA no. 5074 [(b) (4) log no. 7474B]	(b) (4)	Fine, white powder
Potassium Sulfate Lot no. B25N24 BRA no. 3592 Exp. date January 2008 [(b) (4) log no. 7473B]		Fine, white powder
Magnesium Sulfate Lot no. B39142 BRA no. 3780 [(b) (4) log no. 7475B]		Fine, white powder

Methods:

Doses: 1.25, 2.5 and 5 g/kg/day
Basis of Dose Selection: The doses were selected based on the results of a 7-day non-GLP dose range-finding study in dogs (Study No. 382038). In the dose ranging study, animals (n = 2/sex/dose) were treated with BLI800 (5 g/kg/day, Group 2) and vehicle (Group 1) orally by gavage once daily for a minimum of 7 consecutive days. The dosage volume was 15 mL/kg. There was no mortality. Clinical findings included abnormal excreta (soft and/or mucoid feces and/or diarrhea) which were observed throughout the dosing period in the 5.0 g/kg/day group males and females. In addition, increased incidences of emesis and wet clear material around the mouth were also observed throughout the dosing period for these animals. Based on the above findings, the doses for the current study were chosen to demonstrate a gradient of toxic effects. It was anticipated that the high dose level of BLI800 would show drug-specific effects without producing a high incidence of fatalities. Dose levels of 1.25 and 2.5 g/kg/day were selected to be narrow enough to reveal any dose-related trends. The highest tested dose was the MFD based on the solubility of the salts in deionized water.

Species/strain: Beagle dogs
Number/sex/group or time point (main study): 3/sex/group
Route, formulation and dose volume: Oral gavage, solution in water, 15 mL/kg
Satellite groups used for toxicokinetics or recovery: None
Age: Approximately 7 months old

Weight: Males: 7.1-8.8 kg; Females: 6.0-7.2 kg
Study design: The following table (from page 18 of the study report) shows the study design.

Group Number	Test Article	Dosage Level (g/kg/day)[a]	Dosage Volume (mL/kg)	Number of Animals	
				Males	Females
1	Vehicle	0	15	3	3
2	BLI800	1.25	15	3	3
3	BLI800	2.5	15	3	3
4	BLI800	5.0	15	3	3

[a] = Test article formulations were not adjusted to account for test article purity.

Observations and times:

Mortality: Mortality was observed twice daily.

Clinical signs: Clinical signs were observed three times daily.

Body weights: Body weight was recorded on a weekly basis.

Food consumption: Food consumption was recorded on a weekly basis.

Ophthalmoscopy: Ophthalmoscopic examinations were conducted at pretest and during Week 3.

Hematology: Hematology was conducted at necropsy.

Clinical chemistry: Clinical chemistry was conducted at necropsy.

Urinalysis: Urinalysis was conducted at necropsy.

Electrocardiography: Electrocardiography was conducted at Week -1 and Week 3.

Gross pathology: Gross pathology was conducted at necropsy.

Organ weights: The following (from page 31 of the study report) organs were weighed from all animals.

Adrenals
Brain
Heart
Kidneys
Liver
Ovaries
Pituitary
Prostate
Spleen
Testes
Thymus
Thyroid with parathyroids
Uterus with cervix

Histopathology: The following (from page 30 of the study report) organs/tissues from all animals were examined for histopathological examinations.

Adrenals (2)
Aorta
BMDS microchip[a]
Bone with marrow
  Femur
  Sternum
Bone marrow smear (from rib)[b]
Brain
  Cerebrum (2 levels)
  Cerebellum with pons/medulla
Cervix
Epididymides (2)[c]
Eyes with optic nerves (2)[d]
Gallbladder
Gastrointestinal tract
  Esophagus
  Stomach
  Duodenum
  Jejunum
  Ileum
  Cecum
  Colon
  Rectum
Heart
Kidneys (2)
Liver (sections of 2 lobes)
Lungs (including bronchi, fixed by inflation with fixative)
Lymph nodes
  Mandibular
  Mesenteric
Ovaries (2)
Oviducts (2)
Pancreas
Peripheral nerve (sciatic)
Peyer's patches
Pituitary
Prostate
Salivary glands [mandibular (2)]
Skeletal muscle (rectus femoris)
Skin with mammary gland[d]
Spinal cord (cervical, thoracic, lumbar)
Spleen
Testes (2)[c]
Thymus
Thyroids [with parathyroids (2)]
Tongue
Trachea
Ureters (2)
Urinary bladder
Uterus
Vagina
Gross lesions (when possible)

[a] - Not examined microscopically.
[b] - Bone marrow smears were obtained at the scheduled necropsy, but not placed in formalin; slides were examined only if scientifically warranted.
[c] - Fixed in Bouin's solution
[d] - Fixed in Davidson's solution
[e] - For females: a corresponding section of skin was collected from the same anatomic region for males.

Toxicokinetics: None

Results:

Mortality: None

Clinical signs: Test article-related clinical signs consisted of emesis (containing food and/or white, yellow and/or clear material), wet clear material around mouth, excessive salivation, white frothy material around the mouth, excessive drinking of water and abnormal excreta (soft and/or mucoid feces and/or diarrhea). These findings were noted at all doses, with the highest incidence for most of the findings being noted at 5.0 g/kg/day. These findings were noted starting on study day 0 (first day of dosing) as early as 15 minutes post-dosing and persisted up until the 4-hour post-dose observation for the remainder of the study. The following Table (from page 34 of the study report) shows the summary of clinical findings.

Text Table 1. Summary of clinical findings of diarrhea, soft feces and emesis

Summary of Number of Occurrences of Selected Clinical Observations[a]								
	Males				Females			
Dose Level (g/kg/dose)	0	1.25	2.5	5.0	0	1.25	2.5	5.0
Diarrhea	0	41	69	91	2	54	59	80
Soft Feces[b]	4	38	62	44	7	59	46	59
Emesis[c]	2	51	68	149	7	42	109	119

[a] - Clinical observations for detailed physical examinations, prior to dosing, at the time of dosing, 1-2 hours post-dosing and any unscheduled observations
[b] - Soft feces observations include findings of soft feces and mucoid feces
[c] - Emesis observations include findings of emesis containing white, yellow, red and/or food material.

Body weights: The mean initial (Week-1) and final (Week 3) body weights of control males were 8.0 and 8.4 kg, respectively. The mean initial (Week-1) and final (Week 3) weight of control females were 6.5 and 7.0 kg, respectively. There were no significant treatment-related effects.

Food consumption: The mean initial (Week -1 to 0) and final (Week 3 to 4) food consumption in control males were 285 and 352 g/animal/day, respectively. The mean initial (Week -1 to 0) and final (Week 3 to 4) food consumption in control females were 248 and 258 g/animal/day, respectively. There were no significant treatment-related effects.

Ophthalmoscopy: There were no significant treatment-related ocular findings.

Hematology: No significant treatment-related changes were observed.

Clinical chemistry: No significant treatment-related changes were observed.

Urinalysis: Higher pH in males and females was observed in all groups administered BLI800 (at 1.25, 2.5 and 5.0 g/kg/day) on Day 28. The results are shown in the following Table (from page 37 of the study report).

Text Table 2. Higher Urine pH In Dogs Administered BLI800. Study Day 28

Day	-6	-6	28	28
Dosage (g/kg/day):	0	All dogs administered BLI800[a]	0	All dogs administered BLI800[a]
Number of dogs each sex	3	9	3	9
Males	6.3	6.2	7.2	7.7**
Females	5.5	6.0	6.0	7.9**

** = Significantly different from the control group at 0.01 using Dunnett's test

[a] = All dogs administered BLI800 included total of 9 male or female dogs combined, from the 1.25 g/kg/day (n=3 males and n=3 females); 2.5 g/kg/day (n=3 males and n=3 females); and the 5.0 g/kg/day (n=3 males and n=3 females) groups.

In addition, higher urine sodium level and sodium excretion through the urine were also observed in the BLI800 treated animals, as shown in the following Table (from page 39 of the study report).

Text Table 3. Urine Sodium, Sodium Excretion And Sodium Clearance Rates On Study Day 28

	Males				Females			
Dosage (g/kg/day)	0	1.25	2.5	5.0	0	1.25	2.5	5.0
Urine Sodium[a]	3	3	3	3	3	3	3	3
Day -6	62	108	53	55	152	69	85	107
Day 28	96	217	91	141	50	150	105	141
Sodium excretion rate	3	3	3	3	3	3	3	3
Day -6	0.003	0.006	0.005	0.006	0.003	0.002	0.008	0.004
Day 28	0.011	0.022	0.011	0.030	0.006	0.021	0.025	0.019
Sodium clearance rate	3	3	3	3	3	3	3	3
Day -6	0.003	0.005	0.004	0.005	0.003	0.002	0.009	0.004
Day 28	0.009	0.017	0.010	0.022	0.006	0.021	0.024	0.019

[a] = Number of dogs tested per group

Electrocardiography: There were no significant treatment-related findings.

Gross pathology: There were no treatment-related macroscopic observations.

Organ weights: No significant treatment-related effects were observed.

Histopathology: There were no significant treatment-related microscopic observations.

Summary: In a 28-day oral toxicology study in dogs (3 animals/sex/group), animals were treated with BLI800 (combination of sodium sulfate, potassium sulfate and magnesium sulfate) by oral gavage at 1.25, 2.5 and 5.0 g/kg/day. The target organ could not be identified in the absence of any significant organ toxicity. This is to be mentioned here that the sponsor should have used at least four animals per sex per dose.

2.6.6.4 Genetic toxicology

None

2.6.6.5 Carcinogenicity

None

2.6.6.6 Reproductive and developmental toxicology

None

2.6.6.7 Local tolerance

None

2.6.6.8 Special toxicology studies

None

2.6.6.9 Discussion and Conclusions

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). In rats, 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. In rats, the target organs appeared to be the adrenal cortex (alteration of vacuolation), colon (dilated colon), jejunum (dilated) and kidney (minimal mineralization). In dogs, no significant organ toxicities were observed. Clinical signs of diarrhea and electrolyte and metabolic changes appeared to be secondary to the pharmacological actions or homeostatic adaptation to the osmotic load. There appears to be no significant safety concern from a nonclinical standpoint for the proposed indication.

2.6.6.10 Tables and Figures

Incorporated in the appropriate sections of this review

2.6.7 TOXICOLOGY TABULATED SUMMARY

Pivotal toxicology studies were tabulated under section: "**Studies reviewed within this submission**".

OVERALL CONCLUSIONS AND RECOMMENDATIONS

SuPrep® (BLI800) is a liquid concentrate for oral administration that is comprised of 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.

Conclusions: From a nonclinical standpoint, this submission satisfies the criteria for marketing authorization of Suprep and is recommended for approval for the proposed use.

Unresolved Toxicology Issues: None

Recommendations: From a nonclinical standpoint, this NDA may be approved.

Suggested Labeling: The labeling of Suprep conforms to the format specified under 21CFR 201.56(d) and 201.57 for the content and format of labeling for human prescription drugs. However, the sponsor should be asked to modify the proposed label of Suprep as suggested in the text of this review.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

cc:

Original NDA
DGP
DGP/RPM/MScherer
DGP/SChakder
DGP/TChakraborti

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/

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3/6/2009 02:25:47 PM
PHARMACOLOGIST

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