CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202535Orig1s000

PHARMACOLOGY REVIEW(S)

Comments on NDA 202535 Picoprep (sodium picosulfate, magnesium oxide, and citric acid) powder for oral solution

From: Abigail Jacobs, Assoc. Dir. Pharm/Tox
Date: July 16, 2012

1. I concur that there are no nonclinical approval issues for this NDA.
2. I concur that the pregnancy category is "B".
3. I agree that the animal toxicology section should be deleted.
4. My other comments have been discussed with the supervisor and will be addressed as appropriate.

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/s/

ABIGAIL C JACOBS
07/16/2012

ADDENDUM TO PHARMACOLOGIST'S REVIEW OF NDA 202535 (Prepopik, Ferring Pharmaceuticals, Inc.),

Sponsor & Address: Ferring Pharmaceuticals, Inc.
Parisppany, NJ

Reviewer Name: Tamal K. Chakraborti, Ph.D.
Pharmacologist, DGIEP

Date of Submission: September 16, 2011

Date of Receipt: September 16, 2011

Date of Review: July 16, 2012

Drug: Prepopik (Submitted to NDA as PicoPrep)

Category: Stimulant laxative (sodium picosulfate)/osmotic laxative (magnesium citrate)

This addendum is to modify the Executive Summary section of the pharmacology review and the text of the labeling section (8.1 Pregnancy) of the original review dated May 14, 2012. The embryofetal development study in rabbits was not considered adequate, as treatment-related mortalities were observed at all doses. In addition, this addendum also incorporated the structure of the active metabolite, bis(*p*-hydroxyphenyl)-2-pyridylmethane (BHPM), of sodium picosulfate.

Amended Version:

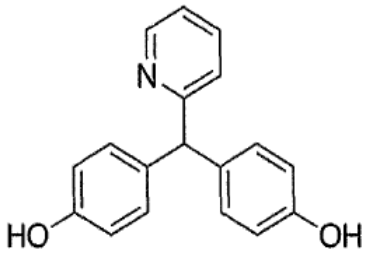
1 Executive Summary

1.1 Introduction

PicoPrep™ (sodium picosulfate, magnesium oxide and citric acid) powder for oral solution is indicated for cleansing of the colon as a preparation for colonoscopy in adults. It is a stimulant cathartic. Sodium picosulfate is converted to the pharmacologically active metabolite, bis(*p*-hydroxyphenyl)-2-pyridylmethane (BHPM), by gut microbes through bacterial hydrolase. It is to be mentioned here that Bisacodyl is also hydrolyzed by colonic bacteria to form the same active metabolite, BHPM. Sodium picosulfate itself is pharmacologically inactive and undergoes very low absorption. Apart from the primary active component sodium picosulfate, which constitutes (b) (4) of the 16.1 g PicoPrep drug product, the product also contains magnesium oxide (22%)

and citric acid (74%), which form magnesium citrate in water solution. The laxative effect of sodium picosulfate is attributable to an inhibition of water absorption in the colon, caused by the diphenol metabolite, BHPM. When the product is dissolved in water, the magnesium oxide and citric acid interact to form magnesium citrate, which is an osmotic laxative. Citric acid and magnesium oxide are extensively used in food products or OTC pharmaceutical products in the United States. Sodium picosulfate is marketed in several countries outside the United States as a stimulant laxative. The following figure (from page 13 of the method validation report No. UA396 in Section 4.2.2.1.1 of the submission) shows the structure of BHPM.

Bis-(p-hydroxyphenyl)-pyridyl-2-methane (BHPM):



Molecular formula (Delivery Form): $C_{18}H_{15}NO_2$
Molecular formula (Analysis Form): $C_{18}H_{15}NO_2$
Molecular weight (Delivery Form): 277.3 g/mol
Molecular weight (Analysis Form): 277.3 g/mol

1.2 Brief Discussion of Nonclinical Findings

The applicant has conducted several nonclinical studies with sodium picosulfate which include 14-day oral toxicology studies in rats and dogs and genotoxicity studies (Ames test, mouse lymphoma assay and *in vivo* mouse micronucleus test). In addition, the applicant also conducted toxicology studies with PicoPrep, the drug product, which include 28-day oral toxicology studies in rats and dogs, and reproductive toxicology studies, i.e., fertility and early embryonic development to implantation study (Segment I) in rats, embryofetal development studies (Segment II) in rats and rabbits and pre and postnatal development study (Segment III) in rats.

The principal active component of PicoPrep, sodium picosulfate, was administered orally (gavage) for up to 14 days at doses (30, 300 and 1000 mg/kg BID) up to 1000 mg/kg BID in rats and at doses (15, 150 and 600 mg/kg BID) up to 600 mg/kg BID in dogs (approximately 6000 and 3600 times the recommended human dose of 10 mg of sodium picosulfate in 16.13 g of drug product/pouch or 0.166 mg/kg of sodium picosulfate based on a 60 kg body weight), respectively. Treatment-related clinical signs included soft stools, diarrhea, and fecal staining, the expected pharmacological responses. In rats, sodium picosulfate caused increase in thickness of the intestine (elongated glandular crypts lined by immature, basophilic, epithelial cells) at all tested

doses, minimal to mild mucosal hyperplasia of the small and large intestine (duodenum, jejunum, ileum, cecum, colon, and rectum) at all doses and mucosal hyperplasia associated with lymphocytic infiltration in the small intestine at ≥ 300 mg/kg BID doses (about 1800 times the recommended human dose of sodium picosulfate).

Sodium picosulfate was not mutagenic in the Ames test, mouse lymphoma assay and did not induce micronuclei in *in vivo* mouse bone marrow micronucleus test.

PicoPrep was administered orally (gavage) for up to 28 days at doses (230, 750 and 2000 mg/kg BID) up to 2000 mg/kg BID in rats and at doses (230, 500 and 1000 mg/kg BID) up to 1000 mg/kg BID in dogs (about 8 and 4 times the recommended human dose, respectively). In a male and female oral fertility study (Segment I) in rats, PicoPrep did not cause any significant adverse effect on male or female fertility parameters up to a maximum dose of 2000 mg/kg BID (about 1.2 times the recommended human dose based on the body surface area). Embryofetal development (Segment II) studies with PicoPrep have been performed in pregnant rats (230, 750 and 2000 mg/kg BID) and rabbits (230, 460 and 900 mg/kg BID) at doses up to 1.2 times and 1.1 times the recommended human dose, respectively, based on the body surface area. In rats, it did not show any evidence of impaired fertility or harm to the fetus. In rabbits, there were treatment-related mortalities at all doses, and thus, the study was not considered adequate. A pre and postnatal development (Segment III) study in rats, PicoPrep (230, 750 and 2000 mg/kg BID doses) showed no evidence of any adverse effect on pre and postnatal development at oral doses up to 2000 mg/kg BID (about 1.2 times the recommended human dose based on the body surface area).

Overall, nonclinical safety of PicoPrep has been adequately tested in several toxicology studies. When PicoPrep, the drug product, was tested in rats and dogs, the NOAELs were 2000 mg/kg BID (about 8 times the recommended clinical dose of 16.1 g BID or 533 mg/kg BID based on a 60-kg body weight) and 1000 mg/kg BID (about 4 times the recommended clinical dose of 16.1 g BID or 533 mg/kg BID based on a 60-kg body weight), respectively. Overall, nonclinical studies conducted with PicoPrep provide adequate assurance of safety and support its proposed use at the intended therapeutic dosage and in accordance with the proposed product labeling.

1.3 Recommendations

1.3.1 Approvability

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

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

The draft labeling of PicoPrep conforms to the content and format specified under 21CFR201.56 and the specific requirements on content and format of labeling for human prescription drugs under 21CFR201.57. However, the following changes should be incorporated.

8.1 Pregnancy

Applicant's Version:

"8.1 ***Pregnancy***

Pregnancy Category B. (b) (4)

Evaluation: The text is in accordance with 21CFR 201.57(f)(6)(i)(b). However, the text should be modified as follows to reflect the dose based on the body surface area calculation. The Segment II rabbit study was not adequate, as there were treatment-related mortalities at all doses. In addition, the findings of the pre and postnatal development study in rats need to be incorporated.

Recommended Version:

"8.1 **Pregnancy**

Pregnancy Category B

Pregnancy Category B

Reproduction studies with PicoPrep have been performed in pregnant rats at oral doses up to 2000 mg/kg/day (about 1.2 times the recommended human dose based on the body surface area), and did not reveal any evidence of impaired fertility or harm to the fetus due to PicoPrep. The reproduction study in rabbits was not adequate, as treatment-related mortalities were observed at all doses. A pre and postnatal development study in rats showed no evidence of any adverse effect on pre and postnatal development at oral doses up to 2000 mg/kg BID (about 1.2 times the recommended human dose based on the body surface area). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, PicoPrep should be used during pregnancy only if clearly needed.

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 PICOPREP is administered to a nursing woman."

Evaluation: The text is in accordance with 21CFR 201.57(f)(8)(iii).

Recommended Version: None

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Applicant's Version:

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

(b) (4)

Evaluation: The format is in accordance with 21CFR 201.57(f)(5). However, the text should be modified to state that genotoxicity studies were conducted with sodium picosulfate (b) (4)

Recommended Version:

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

Long-term studies in animals to evaluate carcinogenic potential or studies to evaluate mutagenic potential have not been performed with PicoPrep. However, sodium picosulfate was not mutagenic in the Ames test, the mouse lymphoma assay and the mouse bone marrow micronucleus test.

In a fertility study in rats, PicoPrep did not cause any significant adverse effect on male or female fertility parameters at oral doses up to 2000 mg/kg BID (about 1.2 times the recommended human dose based on the body surface area)."

(b) (4)

Applicant's Version:

(b) (4)

Evaluation: This section is not needed and should be deleted.

_____ _____
Tamal K. Chakraborti, Ph.D. Date
Pharmacologist

Comment:

_____ _____
Sushanta K. Chakder, Ph.D. Date
Supervisory Pharmacologist

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
07/16/2012

SUSHANTA K CHAKDER
07/16/2012

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:	202535
Supporting document/s:	001
Applicant's letter date:	September 16, 2011
CDER stamp date:	September 16, 2011
Product:	PicoPrep™ (sodium picosulfate, magnesium oxide and citric acid) powder for oral solution
Indication:	PicoPrep™ is indicated for cleansing of the colon as a preparation for colonoscopy in adults
Applicant:	Ferring Pharmaceuticals, Inc.
Review Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Reviewer:	Tamal K. Chakraborti, Ph.D.
Supervisor:	Sushanta K. Chakder, Ph.D.
Division Director:	Donna Griebel, MD
Project Manager:	Maureen Dewey, M.P.H.

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 202535 are owned by Ferring Pharmaceuticals or are data for which Ferring Pharmaceuticals has obtained a written right of reference. Any information or data necessary for approval of NDA 202535 that Ferring Pharmaceuticals 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 202535.

Reference ID: 3130340

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1 Executive Summary

1.1 Introduction

PicoPrep™ (sodium picosulfate, magnesium oxide and citric acid) powder for oral solution is indicated for cleansing of the colon as a preparation for colonoscopy in adults. It is a stimulant cathartic. Sodium picosulfate is converted to the pharmacologically active metabolite, bis(*p*-hydroxyphenyl)-2-pyridylmethane (BHPM), by gut microbes through bacterial hydrolase. It is to be mentioned here that Bisacodyl is also hydrolyzed by colonic bacteria to form the same active metabolite, BHPM. Sodium picosulfate itself is pharmacologically inactive and undergoes very low absorption. Apart from the primary active component sodium picosulfate, which constitutes (b) (4) of the 16.1 g PicoPrep drug product, the product also contains magnesium oxide (22%) and citric acid (74%), which form magnesium citrate in water solution. The laxative effect of sodium picosulfate is attributable to an inhibition of water absorption in the colon, caused by the diphenol metabolite, BHPM. When the product is dissolved in water, the magnesium oxide and citric acid interact to form magnesium citrate, which is an osmotic laxative. Citric acid and magnesium oxide are extensively used in food products or OTC pharmaceutical products in the United States. Sodium picosulfate is marketed in several countries outside the United States as a stimulant laxative.

1.2 Brief Discussion of Nonclinical Findings

The applicant has conducted several nonclinical studies with sodium picosulfate which include 14-day oral toxicology studies in rats and dogs and genotoxicity studies (Ames test, mouse lymphoma assay and *in vivo* mouse micronucleus test). In addition, the applicant also conducted toxicology studies with PicoPrep, the drug product, which include 28-day oral toxicology studies in rats and dogs, and reproductive toxicology studies, i.e., fertility and early embryonic development to implantation study (Segment I) in rats, embryofetal development studies (Segment II) in rats and rabbits and pre and postnatal development study (Segment III) in rats.

The principal active component of PicoPrep, sodium picosulfate, was administered orally (gavage) for up to 14 days at doses (30, 300 and 1000 mg/kg BID) up to 1000 mg/kg BID in rats and at doses (15, 150 and 600 mg/kg BID) up to 600 mg/kg BID in dogs (approximately 6000 and 3600 times the recommended human dose of 10 mg of sodium picosulfate in 16.13 g of drug product/pouch or 0.166 mg/kg of sodium picosulfate based on a 60 kg body weight), respectively. Treatment-related clinical signs included soft stools, diarrhea, and fecal staining, the expected pharmacological responses. Treatment-related clinical chemistry findings in rats include decrease in electrolytes (sodium, potassium and chloride) following administration of PicoPrep. In rats, sodium picosulfate caused increase in thickness of the intestine (elongated glandular crypts lined by immature, basophilic, epithelial cells) at all tested doses, minimal to mild mucosal hyperplasia of the small and large intestine (duodenum,

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jejunum, ileum, cecum, colon, and rectum) at all doses and mucosal hyperplasia associated with lymphocytic infiltration in the small intestine at ≥ 300 mg/kg BID doses (about 1800 times the recommended human dose of sodium picosulfate).

Sodium picosulfate was not mutagenic in the Ames test, mouse lymphoma assay and did not induce micronuclei in *in vivo* mouse bone marrow micronucleus test.

The applicant did not conduct reproductive toxicology studies with sodium picosulfate. However, the applicant provided literature references (Nishimura M, A Kast, and Y Tsunenari, 1977, Iyakuhin Kenkyu, 8:366-396) for the reproductive toxicology studies with sodium picosulfate. In oral fertility studies in rats, there was no significant treatment-related adverse effect of sodium picosulfate at dosage levels up to 100 mg/kg/day on mating performance and fertility. Sodium picosulfate was not teratogenic in rats up to 10,000 mg/kg/day and in rabbits up to 1000 mg/kg/day, PO. In a peri and postnatal development study in rats, animals were treated at 1, 10, and 100 mg/kg/day of sodium picosulfate. There were an increased number of dead pups at birth at 100 mg/kg/day. Postweaning growth, development, behavior and reproductive functions were unaffected by treatment with sodium picosulfate.

PicoPrep was administered orally (gavage) for up to 28 days at doses (230, 750 and 2000 mg/kg BID) up to 2000 mg/kg BID in rats and at doses (230, 500 and 1000 mg/kg BID) up to 1000 mg/kg BID in dogs (about 8 and 4 times the recommended human dose, respectively). In a male and female oral fertility study (Segment I) in rats, PicoPrep did not cause any significant adverse effect on male or female fertility parameters up to a maximum dose of 2000 mg/kg BID (about 1.2 times the recommended human dose based on the body surface area). Embryofetal development (Segment II) studies with PicoPrep have been performed in pregnant rats (230, 750 and 2000 mg/kg BID) and rabbits (230, 460 and 900 mg/kg BID) at doses up to 1.2 times and 1.1 times the recommended human dose, respectively, based on the body surface area and have revealed no evidence of impaired fertility or harm to the fetus due to PicoPrep. A pre and postnatal development (Segment III) study in rats, PicoPrep (230, 750 and 2000 mg/kg BID doses) showed no evidence of any adverse effect on pre and postnatal development at oral doses up to 2000 mg/kg BID (about 1.2 times the recommended human dose based on the body surface area).

Overall, nonclinical safety of PicoPrep has been adequately tested in several toxicology studies. When PicoPrep, the drug product, was tested in rats and dogs, the no-observed-adverse-effect-levels (NOAELs) were 2000 mg/kg BID (about 8 times the recommended clinical dose of 16.1 g BID or 533 mg/kg BID based on a 60-kg body weight) and 1000 mg/kg BID (about 4 times the recommended clinical dose of 16.1 g BID or 533 mg/kg BID based on a 60-kg body weight), respectively. Overall, nonclinical studies conducted with PicoPrep provide adequate assurance of safety and support its proposed use at the intended therapeutic dosage and in accordance with the proposed product labeling.

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1.3 Recommendations

1.3.1 Approvability

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

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

The draft labeling of PicoPrep conforms to the content and format specified under 21CFR201.56 and the specific requirements on content and format of labeling for human prescription drugs under 21CFR201.57. However, the following changes should be incorporated.

8.1 Pregnancy

Applicant's Version:

"8.1 ***Pregnancy***

Pregnancy Category B. (b) (4)

Evaluation: The text is in accordance with 21CFR 201.57(f)(6)(i)(b). However, the text should be modified as follows to reflect the dose based on the body surface area calculation. In addition, the findings of the pre and postnatal development study in rats need to be incorporated.

Recommended Version:

"8.1 **Pregnancy**

Pregnancy Category B

Reproduction studies with PicoPrep have been performed in pregnant rats at oral doses up to 2000 mg/kg/day (about 1.2 times the recommended human dose based on the body surface area) and in rabbits at oral doses up to 900 mg/kg BID (about 1.1 times the recommended human dose based on the body surface area). These studies did not reveal any evidence of impaired fertility or harm to the fetus due to PicoPrep. A pre and postnatal development study in rats showed no evidence of any adverse effect on pre and postnatal development at oral doses up to 2000 mg/kg BID (about 1.2 times the recommended human dose based on the body surface area). There are, however, no

adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, PicoPrep should be used during pregnancy only if clearly needed."

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 PICOPREP is administered to a nursing woman."

Evaluation: The text is in accordance with 21CFR 201.57(f)(8)(iii).

Recommended Version: None

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Applicant's Version:

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

[redacted] (b) (4)

Evaluation: The format is in accordance with 21CFR 201.57(f)(5). However, the text should be modified to state that genotoxicity studies were conducted with sodium picosulfate [redacted] (b) (4)

Recommended Version:

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

Long-term studies in animals to evaluate carcinogenic potential or studies to evaluate mutagenic potential have not been performed with PicoPrep. However, sodium picosulfate was not mutagenic in the Ames test, the mouse lymphoma assay and the mouse bone marrow micronucleus test.

In a fertility study in rats, PicoPrep did not cause any significant adverse effect on male or female fertility parameters at oral doses up to 2000 mg/kg BID (about 1.2 times the recommended human dose based on the body surface area)."

(b) (4)

Applicant's Version:

(b) (4)

Evaluation: This section is not needed and should be deleted.

2 Drug Information

2.1 Drug

CAS Registry Number:

Sodium Picosulfate: 10040-45-6 (anhydrous)
Magnesium Oxide: 1309-48-4
Citric Acid: 77-92-9

Generic Name: Sodium picosulfate, Magnesium oxide, Citric acid

Code Name: N/A

Chemical Name:

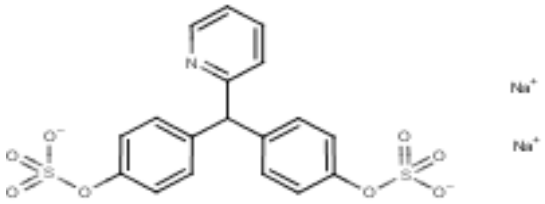
Sodium Picosulfate: 4,4'-[(pyridin-2-yl)methylene]diphenyl bis(sodium sulphate) monohydrate
Magnesium Oxide: Magnesium oxide
Citric Acid: 1,2,3-propanetricaboxylic acid, 2-hydroxy

Molecular Formula/Molecular Weight:

Sodium picosulfate: $C_{18}H_{13}NNa_2O_8S_2$/499.4
Magnesium Oxide: MgO/40.31
Citric acid: $C_6H_8O_7$/192.14

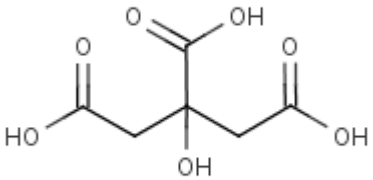
Structure:

Sodium picosulfate:



Magnesium oxide: Mg=O

Citric acid:



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Pharmacologic Class: Stimulant laxative (sodium picosulfate)/osmotic laxative (magnesium citrate)

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

IND 101738 (PicoPrep, Ferring Pharmaceuticals, Inc.)

2.3 Drug Formulation

PicoPrep powder for oral solution is a white crystalline powder with a faint odor of orange. PicoPrep is provided as a powder in two pouches, the contents of each to be dissolved in 5 ounces (150 mL) of cold water and consumed. Each pouch contains 16.1 (b) (4) g of powder, which has three active ingredients: sodium picosulfate 10 mg; magnesium oxide 3.5 g and citric acid 12 g, which together form magnesium citrate in solution. The following table (from page 1 of 2.3.P.1 of applicant's submission) shows the composition of the drug product.

Component	Amount per dosage form	Function	Quality standard
Sodium picosulfate	10 mg	Active	Ph. Eur. current edition
Magnesium oxide, (b) (4)	3.5 g	Active	USP current edition
Citric acid, anhydrous	12 g	Active	USP current edition
Potassium hydrogen carbonate (b) (4)	(b) (4)		USP current edition
Saccharin sodium			USP current edition
Orange flavouring, (b) (4) spray dried			FCC

2.4 Comments on Novel Excipients

All excipients met current USP standards. The following Table (from page 1 of 3.2.P.4.1) shows the list of excipients.

Specifications of Excipients

The excipients comply with the following quality standards:

Excipient	Quality standard
Potassium bicarbonate	USP current edition
Saccharin sodium	USP current edition
Orange Flavouring, (b) (4) spray dried	In-house (see overleaf)
(b) (4)	USP current edition

2.5 Comments on Impurities/Degradants of Concern

The following Table (from page 1 of 2.3.P.5) shows the product specification.

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Table 1 PICOPREP specification

Test	Analytical principle	Reference to analytical procedure	Acceptance criteria
Appearance	Visual inspection		White crystalline powder with a faint odour of orange
Identification			
Sodium picosulfate	HPLC	PLU-01	(b) (4)
Magnesium oxide	Chemical reaction	PLU-02	
Citric acid	Chemical reaction	PLU-03	
Assay			
Sodium picosulfate	HPLC	PLU-01	
Magnesium oxide	Titration	PLU-04	
Citric acid	Titration	PLU-05	
Uniformity of dosage units			
Content Uniformity (sodium picosulfate)	HPLC	PLU-01	
Content Uniformity (magnesium oxide)	Titration	PLU-04	
Weight variation (citric acid)	Weighing	USP <905>	
Impurities			
(b) (4)	HPLC	PLU-06	
	HPLC	PLU-06	
Any unknown impurity	HPLC	PLU-06	
Sum of all impurities	HPLC	PLU-06	
Microbial limits			
Total aerobic microbiological count (TAMC)	Microbiological enumeration test	USP <61>	
Total yeast and moulds count (TYMC)	Microbiological enumeration test	USP <61>	
Escherichia coli in 1g	Selective media	USP <62>	

Sodium picosulfate related impurities (b) (4) were presented in the above table.

(b) (4)

(b) (4)

The acceptance criterion for unknown impurities (≤ 0.2%) has been set in accordance with ICH Q3B (R2) *Impurities in New Drug Products*. The acceptance criterion for sum of all impurities (≤ 2.0%) was based on a worst case scenario calculation on exposure of impurities at a maximum daily dose of PicoPrep. The maximum daily dose of PicoPrep contains 20 mg sodium picosulfate hence the maximum daily exposure of impurities is not more than (b) (4) in the worst case scenario. The acceptance criteria for the unknown impurities and the total impurities are acceptable from the nonclinical standpoint.

2.6 Proposed Clinical Population and Dosing Regimen

PicoPrep is indicated for cleansing of the colon as a preparation for colonoscopy in adults. PicoPrep is provided as a powder in two pouches, the contents of each to be dissolved in 5 ounces (150 mL) of cold water and consumed. Each pouch contains

16.1 (b) g of powder, which has three active ingredients: sodium picosulfate 10 mg; magnesium oxide 3.5 g and citric acid 12 g, which together form magnesium citrate in solution. Each pouch should be used as follows:

- Split-Dose regimen: The first PicoPrep pouch is taken the night before the colonoscopy, and the second is taken the next day, in the morning prior to the colonoscopy.
- Day-Before regimen: The first PicoPrep pouch is taken in the afternoon or early evening and the second is taken approximately 6 hours later, the night before the colonoscopy.

2.7 Regulatory Background

The following are the major milestones.

1. IND 101738 was submitted on February 22, 2010
2. Type B meeting was held on April 16, 2009 to obtain comments from the FDA on the adequacy of preclinical and chemistry, manufacturing control (CMC) data for PicoPrep
3. The pre-NDA Type B meeting was held on March 21, 2011 under IND 101738

3 Studies Submitted

3.1 Studies Reviewed

STUDY TITLE	REPORT NO.	PAGE
PHARMACOLOGY		15
PHARMACOKINETICS		16
TOXICOLOGY		17
Subacute/Subchronic/Chronic		17
Rat		
A Rising Dose with a Maximum Tolerated Dose Phase Study of Sodium Picosulfate Administered by Oral Gavage to Rats (Non-GLP)	XHM00036	19
A 14-Day Toxicity Study of Sodium Picosulfate Administered by Oral Gavage to Rats	XHM00037	19
A 14-Day Toxicity Study with 1, 5, and 14 Days of Dose Administration of Sodium Picosulfate Administered by Oral Gavage to Rats with a 14-Day Recovery Period	XHM00042	29
A Rising-Dose and Multiple-Dose Tolerance Study of PicoPrep Administered by Oral Gavage to Rats (non-GLP)	XHM00050	51
A 28-Day Toxicity Study of PicoPrep Administered by Oral Gavage to Rats with a 14-Day Recovery Period	XHM00052	50
Dog		
A Rising Dose with a Maximum Tolerated Dose Phase Study of Sodium Picosulfate Administered by Oral Gavage to Dogs (Non-GLP)	XHM00038	45
A 14-Day Toxicity Study of Sodium Picosulfate Administered by Oral Gavage to Dogs	XHM00039	45

Reference ID: 3130340

A Rising-Dose and Multiple-Dose Tolerance Study of PicoPrep Administered by Oral Gavage to Dogs (non-GLP)	XHM00051	58
A 28-Day Toxicity Study of PicoPrep Administered by Oral Gavage to Dogs with a 14-Day Recovery Period	XHM00053	58
GENOTOXICITY		67
In Vitro		
Ames test, sodium picosulfate	783137	67
Mouse lymphoma assay, sodium picosulfate	783142	71
In Vivo		
Mouse micronucleus test, sodium picosulfate	783158	75
REPRODUCTIVE TOXICITY		77
Rat		
Segment I, PicoPrep	XHM00048	79
Segment II, Dose Range, PicoPrep	XHM00044	80
Segment II, Oral, PicoPrep	XHM00045	84
Segment III, Oral, PicoPrep	XHM00049	98
Rabbit		
Segment II, Dose Range, PicoPrep	XHM00046	92
Segment II, Oral, PicoPrep	XHM00047	91
SPECIAL TOXICOLOGY		109

3.2 Studies Not Reviewed

The following method validation studies were not reviewed.

1. Validation of an LC-MS/MS method for the determination of Picosulfate and its active metabolite Bis-(p-Hydroxypheny1)-Pyridyl-2-methane (BHPM) in rat K2-EDTA plasma (Report No. UA396)
2. Validation of an LC-MS/MS method for the determination of Picosulfate and its active metabolite Bis-(p-Hydroxypheny1)-Pyridyl-2-methane (BHPM) in dog K2-EDTA plasma (Report No. UA397)
3. Validation of an LC-MS/MS method for the determination of Picosulfate in dog K2-EDTA plasma (Report No. N-A-BIO-11-130)
4. Analytical Method Validation and Verification of Stability for Citric Acid in Formulations of PicoPrep in Reverse Osmosis Deionized Water
5. Method Validation and Stability Determination to Support Analysis of Sodium Picosulfate in RODI water Dose Formulations by HPLC-UV for Ferring Pharmaceuticals
6. Analytical Method Validation and Verification of Stability for Sodium Picosulfate in Formulations of PicoPrep in Reverse Osmosis Deionized Water
7. Analytical Method Validation and Verification of Stability for Citric Acid in Formulations of PicoPrep in Reverse Osmosis Deionized Water (Report No. 20000997)
8. Method Validation and Stability Determination to Support Analysis of Sodium Picosulfate in RODI water Dose Formulations by HPLC-UV for Ferring Pharmaceuticals (Report No. XHM00031DX)
9. Analytical Method Validation and Verification of Stability for Sodium Picosulfate in Formulations of PicoPrep in Reverse Osmosis Deionized Water (Report No. XHM00054DX).

Reference ID: 3130340

3.3 Previous Reviews Referenced

Pharmacology review of IND 101738 dated March 23, 2010 was cited and incorporated in appropriate sections of this review.

4 Pharmacology

The applicant did not conduct any pharmacology studies with PicoPrep. However, the applicant cited literature references for the pharmacology of sodium picosulfate. Primary pharmacology and safety pharmacology of sodium picosulfate has been reviewed under the original IND 101738. The reviews are incorporated below from the pharmacology review of IND 101738 dated March 23, 2010.

4.1 Primary Pharmacology

Sodium picosulfate is a bisphenol derivative and is metabolized by fecal bacteria in the colon to form the active compound, BHPM. Un-metabolized sodium picosulfate is inactive (Forth, W, G Nell, W Rummel, and H Andres, 1972, Naunyn-Schmiederberg's Arch Pharmacol, 274:46-53). Only bacterial and non-mucosal hydrolases could activate the parent compound (Hillestad, B, RB Sund, and M Buajordet, 1982, Acta Pharmacol Toxicol, 51:388-394; Anonymous, 1976, Laxoberal-sodium picosulfate, Drug Ther Bull, 14:104). This has been confirmed in both germ-free rats, and rats pretreated with the antibiotic neomycin (Jauch, R, R Hankwitz, K Beschke, and H Pelzer, 1975, Arzneim Forsch Drug Res, 25:1796-1800) where no laxative effects were seen after treatment with sodium picosulfate. In both cases, the feces contained only sodium picosulfate with none of the active diphenol metabolite, and also in both cases there was no laxative effect. The laxative effects of sodium picosulfate have been demonstrated in rats and mice.

Gut transit time was studied in rats [Pala, G. et al. l966. On the laxative properties of sulfuric esters of phenols, with particular reference to 4,4'-(2-picolylidene)-bis-phenylsulfuric acid disodium salt (Picosulfol). Arch.int.Pharmacodyn., 164, 356-369)]. In rats given a single oral dose of 50 mg/kg sodium picosulfate 2 hours before

administration of 1 mL of 6% charcoal suspension, there was a 19% increase in gut transit (percent of the travel made from charcoal in 45 minutes) . When the dose was administered 3 hours before the charcoal, gut transit was increased by 36%. In a further study, sodium picosulfate was given at doses of either 25 or 50 mg/kg at the same time as Indian ink. The ink appeared in excreted feces approximately 400 and 340 minutes later, respectively, compared with over 600 minutes in animals that received Indian ink only. At 50 mg/kg administered 3 hours before the Indian ink, the ink appeared in feces approximately 285 minutes later. These data demonstrated that sodium picosulfate has significant effects on both the consistency of feces and the GI transit.

4.2 Secondary Pharmacology

None

Reference ID: 3130340

4.3 Safety Pharmacology

Neurological Effects: Following single oral doses of sodium picosulfate at 40 and 80 mg/kg, there were no significant adverse effects on behavior in an Irwin screen in mice (Pala, G., Coppi, G. and Crescenzi, E. l966. Arch.int.Pharmacodyn., 164, 356-369).

Cardiovascular Effects: Cardiovascular parameters were examined in anesthetized rats at single intravenous doses of up to 160 mg/kg. Sodium picosulfate did not cause any effects on blood pressure and electrocardiography (ECG) parameters (Pala, G., Coppi, G. and Crescenzi, E. l966. Arch.int.Pharmacodyn., 164, 356-369).

Renal Effects: A single oral dose of 50 mg/kg sodium picosulfate had no diuretic effect in water-loaded rats (Pala, G., Coppi, G. and Crescenzi, E. l966. Arch.int.Pharmacodyn., 164, 356-369).

Gastrointestinal Effects:

In Vitro Hepatotoxicity: Sodium picosulfate has been investigated (Nishikawa, L and Kast, A. l981. Arzneim.Forsch.-Drug Res., 31,321-325; Nishikawa, L & Kast, A. 1981. Arzneim.Forsch.-Drug Res., 31, 1010-1012; Nishikawa, L. l981. Arzneim.Forsch.-Drug Res., 31, 1872-1875) in a series of studies using isolated hepatocytes from fetal or newborn rabbits, rats and humans, and Chang Liver cells. Rabbit hepatocytes were the most sensitive, showing dose-related vacuolic and fatty changes, necrosis, and reduced mitosis at concentrations ≥ 400 ug/mL. Less severe effects were seen with rat cells, and both fetal human and Chang cells were only minimally affected at concentrations up to 2000 and 4000 ug/mL, respectively.

Other: Sodium picosulfate had no antibacterial or antifungal activity *in vitro* (Pala, G., Coppi, G. and Crescenzi, E. l966. Arch.int.Pharmacodyn., 164, 356-369).

5 Pharmacokinetics/ADME/Toxicokinetics

The following is incorporated below from the pharmacology review of IND 101738 dated March 23, 2010.

Reference ID: 3130340

5.1 PK/ADME

Absorption of sodium picosulfate has been investigated in rats following a single oral dose of 100 mg /kg. Sodium picosulfate and it metabolites were not detected in either serum or urine, but high concentrations of sodium picosulfate were found in the feces.

Sodium picosulfate was metabolized by bacteria present in the feces in the colon to form the active compound, 4,4'-dihydroxy-diphenyl-(2-pyridyl)-methane. Un-metabolized sodium picosulfate was found to be inactive. Only bacterial and non-mucosal hydrolases can perform the activation step. The route of excretion was further investigated in fasted adult male rats that received a single oral dose of 100 mg/kg sodium picosulfate. Fecal and urine samples were collected at various time points up to 24 hours after dose administration. The mean recovery of sodium picosulfate in the feces was 73.81 % of administered dose at 24 hours postdose. In addition, 1.8% of hydrolysis product, 4,4'-dihydroxy-diphenyl-(2-pyridyl)-methane, was found in the feces. No sodium picosulfate was recovered in the urine, however, a low concentration (0.067%) of the hydrolysis product was found in the urine.

The potential for the diphenol metabolite of sodium picosulfate to enter the enterohepatic circulation was investigated in rats. There was very little billiary excretion in the first 6 hours after a single oral dose of 31 μmol/kg. However, there was a significant billiary excretion between 6 and 18 hours postdose, when the diphenol was excreted conjugated with glucuronide or sulpfate. Only trace amounts conjugated and free diphenol were found in the urine (about 0.5% of the administered dose). It has also been demonstrated that the conjugated diphenol excreted in the bile can also be deconjugated in the colon in the same way as the parent molecule to generate more of the activate diphenol metabolite. Sodium picosulfate was not reported to be excreted via breast milk.

5.2 Toxicokinetics

(Included in toxicology studies)

6 General Toxicology

6.1 Single-Dose Toxicity

None

6.2 Repeat-Dose Toxicity

<u>14-Day Oral (gavage) Toxicology Study with Sodium Picosulfate in Rats (XHM00037)</u>

The review of this study report is incorporated below from the pharmacology review of the original IND 101738 dated March 23, 2010.

Reference ID: 3130340

Study Title: 14-Day Oral (gavage) Toxicology Study with Sodium Picosulfate in Rats

Reference ID: 3130340

Key Study Findings:

- In a 14-day oral toxicology study in rats, animals were treated with sodium picosulfate at 30, 300 and 1000 mg/kg BID or 60, 600 and 2000 mg/kg/day.
- There was no mortality. Clinical signs included soft stool/diarrhea at 600 and 2000 mg/kg/day.
- Body weights were decreased at all doses in both sexes. However, there were no significant treatment-related effects on food consumption.
- Clinical chemistry findings included increases in phosphorus and potassium at all doses in both sexes.
- Total urine volume was decreased at 600 mg/kg/day females.
- Gross necropsy findings included increased thickness and abnormal contents in the gastrointestinal tract (duodenum, jejunum, ileum, colon, cecum, and rectum) at all doses.
- The target organ appeared to be the small and large intestine (mucosal hyperplasia at all doses and lymphocytic infiltration at ≥ 600 mg/kg/day).
- The NOAEL could not bet determined as treatment-related changes were observed at all doses.

Study No.: XHM00037

Volume # Page #: 3, 1

Conducting Laboratory and Location: (b) (4)

Date of Study Initiation: July 17, 2008

Date of Study Completion: April 9, 2009

GLP Compliance: A statement of compliance was included.

QA Report: yes (X) no ( )

Drug, Lot #, and % Purity: Sodium picosulfate, 651316, 99.2%

Methods:

Doses: 0 (water), 30, 300 and 1000 mg/kg BID or 60, 600 and 2000 mg/kg/day. Doses were administered twice daily 8 hours apart

Basis of dose selection: The dose levels were selected based on results of a dose ranging study with a maximum tolerated dose (MTD) phase study ((b) (4) Study No. XHM000363, the report was not submitted). The high dose for the MTD phase was 2000 mg/kg/day, which caused excessive diarrhea and was therefore considered to be too high for a 14-day repeated dose study. The low-dose level was selected as a 20x the intended clinical dose. Based on this

information, the high-dose level was expected to produce some toxic effects, but not excessive lethality that would prevent meaningful evaluation. The mid-dose level was expected to produce minimal to moderate toxic effects. The low-dose level was expected to produce no observable toxicity.

Species/Strain: Rats/Sprague Dawley

Number/Sex/Group or Time Point (Main Study): 10/sex/dose

Route, Formulation, and Volume: Oral (gavage), solution, 10 mL/kg

Satellite Groups Used for Toxicokinetics or Recovery: None

Age: 8 Weeks

Weight: Males: 230-266 g; Females: 179-209 g

Study Design: The following table (from page 16 of the study report) shows the study design.

Experimental Design

Group No.	No. of Animals		Dose Material	Dose Level (mg/kg/dose)	Dose Volume (mL/kg)	Dose Concentration (mg/mL)
	Males	Females				
1	10	10	RODI Water	0	10	0
2	10	10	Sodium Picosulphate	30	10	3
3	10	10	Sodium Picosulphate	300	10	30
4	10	10	Sodium Picosulphate	1000	10	100

Observation and Times:

Mortality: Twice daily

Clinical Signs: Twice daily

Body Weights: Weekly

Food Consumption: Weekly

Ophthalmoscopy: Day-3 and Day 14

Hematology: At necropsy

Reference ID: 3130340

Clinical Chemistry: At necropsy

Urinalysis: At necropsy

Gross Pathology: At necropsy

Organ Weights: The following (from page 20 of the report) organs were weighed from all animals at necropsy.

7.1.7.2. Organ Weights

The following organs were weighed for all animals at scheduled euthanasia:

Organ Weights

Adrenal gland[a]	Prostate gland
Brain	Salivary gland[a]
Epididymis[a]	Seminal vesicles[a]
Heart	Spleen
Kidney[a]	Testis[a]
Liver	Thymus
Lung	Thyroid gland with parathyroid gland[a]
Ovary[a]	
Pituitary gland	Uterus
[a]Paired organ weight.	

Histopathology: The following (from page 21 of the study report) tissues were examined from the control and the high dose groups. The duodenum, jejunum, ileum, colon, cecum, and rectum were identified as target organs in Group 4 and, therefore, were processed and examined from the Group 2 and 3 animals.

Tissue Collection and Preservation

Adrenal gland (paired)	Mammary gland
Animal identification	Nerve, optic[b]
Aorta	Nerve, sciatic
Bone, femur	Ovary (paired)
Bone, sternum	Pancreas
Bone marrow, sternum	Parathyroid gland[c]
Bone marrow smear[a]	Pituitary gland
Brain (cerebrum, cerebellum, brain stem, medulla)	Prostate gland
Cervix	Salivary gland (paired)
Epididymis (paired)	Seminal vesicle (paired)
Esophagus	Skeletal muscle (thigh)
Eye (paired)[b]	Skin (mammary)
Harderian gland (paired)	Spinal cord (cervical, thoracic, lumbar)
Heart	Spleen
Intestine, cecum	Stomach (nonglandular and glandular)
Intestine, colon	Testis (paired)
Intestine, duodenum	Thymus
Intestine, ileum with Peyer's patch[c]	Thyroid gland (paired)
Intestine, jejunum	Tongue
Intestine, rectum	Trachea
Kidney (paired)	Urinary bladder
Liver	Uterus
Lung	Vagina
Lymph node, mandibular	Gross lesions/masses
Lymph node, mesenteric	

[a]Bone marrow smears were collected from the femur at scheduled necropsies only (for possible examination).
[b]Preserved in Davidson's fixative and then transferred to 10% neutral buffered formalin.
[c]Examined only if present in the routine section.

Toxicokinetics: None

Results:

Mortality: None

Clinical Signs: Test article-related clinical observations were limited to expected pharmacological responses of soft/mucoid stools and diarrhea that were observed in a dose-related fashion at the 600 and 2000 mg/kg/day.

Body Weights: The mean initial (Day 1) and final (Day 14) body weights of the control males were 253 and 346 g, respectively. The mean initial (Day 1) and final (Day 14) body weights of the control females were 197 and 251 g, respectively. In males, final body weights were 94%, 90%, 88% of control at low-, mid- and high-dose, respectively. In females, final body weights were 93%, 90% and 93% of control at low-, mid- and high-dose, respectively.

Food Consumption: The mean initial (Day 1-8) and final (Day 8-14) food consumption in control males were 29 and 30 g/animal/day, respectively. The mean initial (Day 1-8) and final (day 8-14) food consumption in control females were 22 and 24 g/animal/day, respectively. There were no significant treatment-related effects on food consumption.

Ophthalmoscopy: There were no test article-related ophthalmic changes noted during the study.

Hematology: There were several slight increases (statistically significant) in hematology parameters (erythrocytes except at 2000 mg/kg/day females, hemoglobin, and hematocrit) for all test article-treated males and females as compared to controls. However, all increases were well within the normalized historical control range. Similarly, there were slight increases in leukocytes, lymphocytes, and monocytes. In addition, there were increases in segmented neutrophils for all test article-treated males and females. However, all increases in total or individual leukocyte populations were within the normalized historical control ranges. There were no clear dose-responses. Overall, these changes were not considered meaningful. Hematology changes are shown in the following table (from page 27-28 of the report).

Statistically Significant Differences in Hematology and Coagulation Parameters (Males)

Sex	Day	Parameter	Group	Statistically Significant Value	Concurrent Control Value	Historical Control Normalized Range
Males	15	Erythrocytes	Group 2 ↑	7.63	6.93	6.510 – 8.700
			Group 3 ↑	7.64		
			Group 4 ↑	7.37		
		Hemoglobin	Group 2 ↑	15.5	14.0	13.00 – 17.50
			Group 3 ↑	15.3		
			Group 4 ↑	14.8		
		Hematocrit	Group 2 ↑	44.5	39.8	37.50 – 47.40
			Group 3 ↑	44.4		
			Group 4 ↑	42.4		
		MCHC	Group 3 ↓	34.5	35.2	33.30 – 38.00
		Leukocytes	Group 2 ↑	10.82	5.41	5.29 – 18.27
			Group 3 ↑	10.63		
			Group 4 ↑	9.21		
		Lymphocytes	Group 2 ↑	9.06	4.30	3.88 – 14.20
			Group 3 ↑	8.72		
			Group 4 ↑	6.63		
		Monocytes	Group 2 ↑	0.26	0.10	0.10 – 0.79
			Group 3 ↑	0.25		
			Group 4 ↑	0.22		
		Segd Neutrophils	Group 4↑	2.21	0.92	0.65 – 4.08
		Basophils	Group 2 ↑	0.03	0.01	0.01 – 0.12
			Group 3 ↑	0.02		

Group 2 (30 mg/kg/day) Group 3 (300 mg/kg/day) Group 4 (1000 mg/kg/day)

Statistically Significant Differences in Hematology and Coagulation Parameters (Females)

Sex	Day	Parameter	Group	Statistically Significant Value	Concurrent Control Value	Historical Control Normalized Range
Females	15	Erythrocytes	Group 2 ↑	7.49	6.89	6.250 – 8.560
			Group 3 ↑	7.55		
		Hemoglobin	Group 2 ↑	15.0	13.9	12.50 – 16.80
			Group 3 ↑	15.2		
			Group 4 ↑	14.7		
		Hematocrit	Group 2 ↑	42.2	38.8	34.90 – 45.40
			Group 3 ↑	42.3		
			Group 4 ↑	41.4		
		Activated PTT	Group 2 ↓	13.0	21.7	8.25 – 38.70
			Group 4 ↓	15.8		
		Leukocytes	Group 2 ↑	9.36	5.93	3.48 – 15.68
			Group 3 ↑	10.65		
		Lymphocytes	Group 2 ↑	7.95	4.96	2.79 – 12.18
			Group 3 ↑	9.15		
		Monocytes	Group 2 ↑	0.19	0.10	0.05 – 0.62
			Group 3 ↑	0.18		
		Segd Neutrophils	Group 4↑	1.79	0.76	0.35 – 4.03
		Basophils	Group 2 ↑	0.02	0.01	0.00 – 0.09
			Group 3 ↑	0.03		

Group 2 (30 mg/kg/day) Group 3 (300 mg/kg/day) Group 4 (1000 mg/kg/day)

Clinical Chemistry: There were increases in phosphorus in all treated males and for the 2000 mg/kg/day females. In addition, there were increases in potassium for all treated males and females. As per the sponsor, these changes were considered secondary findings to slight or mild dehydration from the expected pharmacological effects of the test article. These serum chemistry changes are shown in the following table (from page 29 of the study report).

Statistically Significant Differences in Clinical Chemistry Parameters

Sex	Day	Parameter	Group	Statistically Significant Value	Concurrent Control Value	Historical Control Normalized Range
Males	15	AST	Group 2 ↓	73	102	50.0 – 99.0
		ALK Phos'tase	Group 2 ↓	165	229	100.0 – 226.0
			Group 3 ↓	165		
			Group 4 ↓	179		
		Creatinine	Group 2 ↓	0.26	0.31	0.220 – 0.320
			Group 3 ↓	0.26		
		Calcium	Group 2 ↑	10.10	9.58	9.380 – 10.360
			Group 3 ↑	9.93		
		Phosphorus	Group 2 ↑	8.52	7.95	7.670 – 9.530
			Group 3 ↑	8.80		
			Group 4 ↑	8.59		
		Sodium	Group 2 ↓	144	146	140.0 – 147.0
			Group 4 ↓	143		
		Potassium	Group 2 ↑	5.26	4.52	4.280 – 5.040
			Group 3 ↑	5.11		
			Group 4 ↑	4.91		
		Chloride	Group 2 ↓	104	106	100.0 – 107.0
			Group 4 ↓	104		
Females	15	ALK Phos'tase	Group 2 ↓	94	125	67.0 – 150.0
		Triglyceride	Group 2 ↑	38	24	20.0 – 40.0
		Urea Nitrogen	Group 2 ↓	19	24	14.0 – 19.0
			Group 3 ↓	18		
		Creatinine	Group 2 ↓	0.29	0.38	0.250 – 0.380
			Group 3 ↓	0.28		
			Group 4 ↓	0.31		
		Calcium	Group 2 ↑	10.09	9.73	9.490 – 10.410
			Group 3 ↑	10.20		
			Group 4 ↑	10.16		
		Phosphorus	Group 4 ↑	8.96	7.94	6.890 – 8.600
		Potassium	Group 2 ↑	5.06	4.26	3.890 – 4.790
			Group 3 ↑	4.90		
			Group 4 ↑	4.69		

Group 2 (30 mg/kg/day) Group 3 (300 mg/kg/day) Group 4 (1000 mg/kg/day)

Urinalysis: Total urine volume was decreased at 600 mg/kg/day females. There were no other significant treatment-related changes.

Gross Pathology: Test article-related findings included increased thickness and abnormal contents in the gastrointestinal tract (duodenum, jejunum, ileum, colon, cecum, and rectum) in all test article groups. Increased thickness generally correlated microscopically with mucosal hyperplasia observed during histopathological evaluation. The following table (from page 31 of the study report) shows the gross necropsy findings.

Gross (Internal) Necropsy Findings for Main Study Animals (Males)

Sex	Day	Finding	Group 1	Group 2	Group 3	Group 4
Males	15	Cecum – content abnormal	--	1/10	4/10	2/10
		Colon – thickened	--	--	--	1/10
		Colon - content abnormal	--	1/10	1/10	--
		Epididymides – small	--	--	--	1/10
		Ileum – thickened	--	--	--	1/10
		Jejunum – diverticulum	1/10	--	--	--
		Kidney – dilated pelvis	--	--	--	1/10
		Kidney – focus	--	--	--	1/10
		Large intestine – thickened	--	2/10	1/10	6/10
		Large intestine – content abnormal	--	7/10	4/10	8/10
		Lymph node, mandibular – foci	--	1/10	--	--
		Rectum – content abnormal	--	1/10	2/10	--
		Small intestine – thickened	--	1/10	2/10	3/10
		Small intestine – content abnormal	--	1/10	2/10	4/10
		Stomach, Glandular – focus	--	--	--	1/10
		Testes – small	1/10	--	--	1/10
		Thymus – foci	1/10	1/10	--	--
Females	15	Cecum – content abnormal	--	1/10	2/10	3/10
		Colon – thickened	--	--	--	1/10
		Colon – content abnormal	--	1/10	--	--
		Ileum – diverticulum	--	--	--	1/10
		Ileum – content abnormal	--	1/10	2/10	--
		Jejunum – content abnormal	--	--	--	1/10
		Large intestine – thickened	--	2/10	3/10	2/10
		Large intestine – content abnormal	--	6/10	8/10	6/10
		Lung – discoloration	1/10	--	--	--
		Lymph node, mandibular – foci	1/10	--	--	--
		Rectum – content abnormal	--	2/10	1/10	2/10
		Small intestine – thickened	--	--	1/10	--
		Small intestine – content abnormal	--	1/10	--	2/10
		Spleen – discoloration	--	1/10	--	1/10
		Stomach – foci	--	--	1/10	--
Group 1 (0 mg/kg/day) Group 2 (30 mg/kg/day) Group 3 (300 mg/kg/day) Group 4 (1000 mg/kg/day)						

Organ Weights: Several organ weights (absolute and relative) were decreased as shown in the following table (from page 32 of the study report). However, these changes were not considered treatment-related in the absence of any significant histopathology findings in these organs.

Statistically Significant Differences in Organ Weights

Sex	Day	Organ	Absolute Weight	Relative to Body Weight	Relative to Brain Weight
Males	Day 15	Thyroid Glands	Group 3, 4 ↓	--	--
		Heart	Group 3, 4 ↓	--	--
		Liver	Group 2, 3, 4 ↓	--	Group 2, 3, 4 ↓
		Lungs	Group 4 ↓	Group 3 ↑	--
		Spleen	Group 2, 3, 4 ↓	Group 2, 4 ↓	Group 2, 3, 4 ↓
		Adrenals	--	Group 4 ↑	--
		Brain	--	Group 2, 3, 4 ↑	--
		Testes	--	Group 2, 3 ↑	--
Females	Day 15	Pituitary	Group 3, 4 ↓	--	--
		Adrenals	--	Group 2, 4 ↑	--
		Brain	--	Group 2, 3, 4 ↑	--
		Heart	--	Group 4 ↓	--
Group 2 (30 mg/kg/day) Group 3 (300 mg/kg/day) Group 4 (1000 mg/kg/day)					

Histopathology: Treatment-related changes were seen in the small intestine and large intestine (mucosal hyperplasia characterized by elongated glandular crypts lined by immature, basophilic, epithelial cells) at ≥ 60 mg/kg/day. The incidence and severity of mucosal hyperplasia in the intestines are summarized in the table (page 33 of the study report) below.

Incidence and Severity of Test Article-Related Mucosal Hyperplasia in the Intestines (Day 15)

	Males				Females			
Group	1	2	3	4	1	2	3	4
Dose (mg/kg/dose)	0	30	300	1000	0	30	300	1000
No. animals examined	10	10	10	10	10	10	10	10
Mucosal Hyperplasia								
Duodenum	(0)	(4)	(8)	(7)	(0)	(3)	(7)	(7)
Minimal	0	3	3	5	0	3	3	4
Mild	0	1	5	2	0	0	4	3
Jejunum	(0)	(5)	(8)	(5)	(0)	(4)	(5)	(5)
Minimal	0	4	5	3	0	3	3	5
Mild	0	1	3	2	0	1	2	0
Ileum	(0)	(5)	(7)	(5)	(0)	(0)	(7)	(9)
Minimal	0	3	2	3	0	0	4	5
Mild	0	2	5	2	0	0	3	4
Colon	(0)	(5)	(4)	(2)	(0)	(2)	(3)	(3)
Minimal	0	5	1	2	0	2	3	3
Mild	0	0	3	0	0	0	0	0
Cecum	(0)	(7)	(8)	(7)	(0)	(3)	(6)	(6)
Minimal	0	4	5	6	0	3	5	2
Mild	0	3	3	1	0	0	1	4
Rectum	(0)	(8)	(10)	(9)	(0)	(5)	(7)	(9)
Minimal	0	4	4	8	0	3	4	7
Mild	0	4	6	1	0	2	3	2

In addition, lymphoplasmacytic infiltration characterized by increased numbers of lymphocytes and plasma cells in the lamina propria of villi and deep mucosal interstitium was seen in the small intestine at ≥ 600 mg/kg/day. The incidence and severity of lymphoplasmacytic infiltration in the small intestines are summarized in table (from page 34 of the study report) below.

Incidence and Severity of Test Article-Related Lymphoplasmacytic Infiltration in the Small Intestines (Day 15)

	Males				Females			
Group	1	2	3	4	1	2	3	4
Dose (mg/kg/dose)	0	30	300	1000	0	30	300	1000
No. animals examined	10	10	10	10	10	10	10	10
Lymphoplasmacytic Infiltration								
Duodenum	(0)	(0)	(4)	(3)	(0)	(0)	(4)	(5)
Minimal	0	0	4	3	0	0	4	5
Jejunum	(0)	(0)	(3)	(2)	(0)	(0)	(1)	(1)
Minimal	0	0	3	2	0	0	1	1
Ileum	(0)	(0)	(2)	(2)	(0)	(0)	(1)	(5)
Minimal	0	0	0	0	0	0	1	3
Mild	0	0	2	2	0	0	0	2

Summary: In a 14-day oral (gavage) toxicology study in rats, animals were treated with sodium picosulfate at 30, 300 and 1000 mg/kg BID (twice daily, 8 hours apart) or 60, 600 and 2000 mg/kg/day. The target organ appeared to be the small and large intestine. The NOAEL could not be determined as treatment-related changes were observed at all doses. However, 30 mg/kg/day may be considered as a tolerated dose. The sponsor did not conduct any TK analysis and should be asked to do so.

14-Day Oral (gavage) Toxicology Study with 1, 5, and 14 days of Sodium Picosulfate in Rats with a 14-Day Recovery Period (XHM00042)

The review of this study report is incorporated below from the pharmacology review of IND 101738 dated March 23, 2010.

Reference ID: 3130340

Study Title: 14-Day Oral (gavage) Toxicology Study with 1, 5, and 14 days of Sodium Picosulfate in Rats with a 14-Day Recovery Period

Key Study Findings:

- Clinical signs included soft/mucoid stools at 1.5, 15, 30 and 300 mg/kg BID doses (8 hours apart) or 3, 30, 60 and 600 mg/kg/day
- Body weight and body weight gain were decreased at 60 and 600 mg/kg/day
- Target organs appeared to be the intestine (mucosal hyperplasia, submucosal edema, and lymphoplasmacytic infiltration). The incidences and severity of histopathology findings were greater in females than males. Following the 14-day recovery periods, all histopathology findings were recovered except for females in the cecum.
- The NOAEL could not be determined, as treatment-related adverse effects were observed at all doses.

Study No.: XHM00042

Volume # Page #: 5-11

Conducting Laboratory and Location: (b) (4)

Date of Study Initiation: October 22, 2008

Date of Study Completion: April 23, 2009

GLP Compliance: A statement of compliance was included.

QA Report: yes (X) no ( )

Drug, Lot #, and % Purity: Sodium picosulfate, 651316, 99.2%

Methods: This study has 3 phases (A, B and C). In Phase A, drug was administered for 1 day. In Phase B, the drug was administered for 5 days and in Phase C the drug was administered for 14 days.

Doses: 0 (water), 1.5, 15, 30 and 300 mg/kg BID or 3, 30, 60 and 600 mg/kg/day. Doses were administered twice daily 8 hours apart.

Basis of dose selection: The dose levels were selected based on information from the previous 14-day study (Study No. XHM00037). Soft mucoid stools and diarrhea were observed in the previous study at 60, 600, and 2000 mg/kg/day. Histopathology revealed mucosal hyperplasia in the intestines which was observed at 60, 600, and 2000 mg/kg/day and lymphoplasmacytic infiltration which was observed at 600 and 2000 mg/kg/day. The high-dose (Group 5) was expected to produce mild intestinal histopathology effects. The mid-dose (Group 4) was expected to produce minimal to mild effects. The Group 2 and Group 3 dose levels were expected to produce no observable toxicity.

Species/Strain: Rat/Sprague Dawley

Number/Sex/Group or Time Point (Main Study): 10/sex/dose

Route, Formulation, and Volume: Oral (gavage), solution, 10 mL/kg

Satellite Groups Used for Recovery: Yes

Age: 7 Weeks

Weight: Males: 240-276 g; Females: 173-210 g

Study Design: The following table (from page 15 of the report) shows the study design.

Experimental Design

	No. of Animals														
	Males						Females								
Study Phase:	Phase A		Phase B		Phase C		Phase A		Phase B		Phase C		Dose Material	Dose Level (mg/kg/dose)	Dose Volume (mL/kg)	Dose Conc. (mg/mL)
Phase	Main (Rec)		Main (Rec)		Main (Rec)		Main (Rec)		Main (Rec)		Main (Rec)					
Group 1	10	(5)	10	(5)	10	(5)	10	(5)	10	(5)	10	(5)	RODI Water	0	10	0
Group 2	10	(5)	10	(5)	10	(5)	10	(5)	10	(5)	10	(5)	Sodium Picosulphate	1.5	10	0.15
Group 3	10	(5)	10	(5)	10	(5)	10	(5)	10	(5)	10	(5)	Sodium Picosulphate	15	10	1.5
Group 4	10	(5)	10	(5)	10	(5)	10	(5)	10	(5)	10	(5)	Sodium Picosulphate	30	10	3
Group 5	10	(5)	10	(5)	10	(5)	10	(5)	10	(5)	10	(5)	Sodium Picosulphate	300	10	30
Dosing Day(s)	1		1-5		1-14		1		1-5		1-14					
Euthanasia Day	2	15	6	20	15	29	2	15	6	20	15	29				

Rec = Recovery Phase
Note: Each group consisted of 10 animals/sex/group for the main phase with an additional 5 animals/sex/group designated for the recovery phase. Each group had a 14-day recovery phase following the last day of dose administration.

Observation and Times:

Mortality: Twice daily

Clinical Signs: Detailed clinical observations were performed once daily on Days -11-2 and 1-15 for Phase A, once daily on Days -11-2 and 1-20 for Phase B, and once daily on Days -11-2 and 1-29 for Phase C.

Body Weights: Body weights were recorded on Days -1/-2, 1, 8, and 14 for Phase A, Days -1/-2, 1,5, 8, 14, and 19 for Phase B, and Days -1/-2, 1,8, 14,21, and 28 for Phase C. Final body weights were recorded on Days 2 (Phase A Main), 6 (Phase B Main), 15 (Phase C Main and Phase A Recovery), 20 (Phase B Recovery), and 29 (Phase C Recovery).

Food Consumption: Food consumption measurements were recorded on Days 1, 8, and 14 for Phase A, Days 1, 5, 8, 14, and 19 for Phase B, and Days 1, 8, 14,21, and 28 for Phase C.

Hematology, Clinical Chemistry and Urinalysis: Samples were collected according to the following (from page 25 of the report) schedule.

Samples for Clinical Pathology Evaluation

Group Nos.	Time Point	Hematology	Coagulation	Clinical Chemistry	Urinalysis
Phase A Main 1-5[a]	Day 2	x	x	x	x
Phase B Main 1-5[a]	Day 6	x	x	x	x
Phase C Main and Phase A Recovery 1-5[a]	Day 15	x	x	x	x
Phase B Recovery 1-5	Day 20	x	x	x	x
Phase C Recovery 1-5	Day 29	x	x	x	x

Note: "x" = scheduled sample collection.
[a]Samples were only collected from those animals scheduled for euthanasia.

Gross Pathology, Organ weights and histopathology: Terminal procedures are shown in the following table (from page 27 of the report).

Terminal Procedures

Group No.	No. of Male/Female Rats per Euthanasia Day						Terminal Procedures			Histopathology		
	Phase A		Phase B		Phase C					Phase A	Phase B	Phase C
	Day 2	Day 15	Day 6	Day 20	Day 15	Day 29	Gross Necropsy	Tissue Collection	Organ Weights	Days 2 and 15	Days 6 and 20	Days 15 and 29
1	10/10	5/5	10/10	5/5	10/10	5/5	x	x	x	Limited	Limited	Limited
2	10/10	5/5	10/10	5/5	10/10	5/5	x	x	x	Limited	Limited	Limited
3	10/10	5/5	10/10	5/5	10/10	5/5	x	x	x	Limited	Limited	Limited
4	10/10	5/5	10/10	5/5	10/10	5/5	x	x	x	Limited	Limited	Limited
5	10/10	5/5	10/10	5/5	10/10	5/5	x	x	x	Limited	Limited	Limited

Note: "x" = procedure conducted.
Limited = small intestine (duodenum, jejunum, and ileum) and large intestine (cecum, colon, and rectum).

Organ Weights: The following (from page 28 of the report) organs were weighed for all main phase animals.

Organ Weights

Adrenal gland[a]	Prostate gland
Brain	Salivary gland[a]
Epididymis[a]	Seminal vesicles[a]
Heart	Spleen
Kidney[a]	Testis[a]
Liver	Thymus
Lung	Thyroid gland with parathyroid gland[a]
Ovary[a]	
Pituitary gland	Uterus

[a]Paired organ weight.

Histopathology: The following (from page 29 of the study report) tissues were examined from all main phase animals.

Tissue Collection and Preservation

Adrenal gland (paired)	Mammary gland
Animal identification	Nerve, optic[b]
Aorta	Nerve, sciatic
Bone, femur	Ovary (paired)
Bone, sternum	Pancreas
Bone marrow, sternum	Parathyroid gland[c]
Bone marrow smear[a]	Pituitary gland
Brain (cerebrum, cerebellum, brain stem, medulla)	Prostate gland
Cervix	Salivary gland (paired)
Epididymis (paired)	Seminal vesicle (paired)
Esophagus	Skeletal muscle (thigh)
Eye (paired)[b]	Skin (mammary)
Harderian gland (paired)	Spinal cord (cervical, thoracic, lumbar)
Heart	Spleen
Intestine, cecum	Stomach (nonglandular and glandular)
Intestine, colon	Testis (paired)
Intestine, duodenum	Thymus
Intestine, ileum with Peyer's patch[c]	Thyroid gland (paired)
Intestine, jejunum	Tongue
Intestine, rectum	Trachea
Kidney (paired)	Urinary bladder
Liver	Uterus
Lung	Vagina
Lymph node, mandibular	Gross lesions/masses
Lymph node, mesenteric	

[a]Bone marrow smears were collected from the femur at scheduled necropsies only (for possible examination).
[b]Preserved in Davidson's fixative and then transferred to 10% neutral buffered formalin.
[c]Examined only if present in the routine section.

Toxicokinetics: None

Results:

Mortality: None (all phases)

Clinical Signs:

Phase A (Single Dose): Test article-related clinical observations were limited to transient soft/mucoid stools that were observed in a dose-related fashion for all test article-treated groups (Groups 2-5: 1.5, 15, 30, and 300 mg/kg/dose BID, respectively). Gastrointestinal disturbances subsided after cessation of dose administration by Day 3 for Group 2 and by Day 6 in the remaining Groups 3-5 during the recovery period.

Phase B (5-Day repeated dose): Test article-related clinical observations were limited to soft/mucoid stools and diarrhea that were generally observed in a dose-related fashion for all test article-treated groups (Groups 2-5: 1.5, 15, 30, and 300

mg/kg/dose BID, respectively). In addition, fecal stain was observed in Group 3-5 males and females and dehydration was observed in one Group 5 male. Gastrointestinal disturbances subsided after cessation of dose administration by Day 7 for Group 2 and by Day 10 in the remaining Groups 3-5 during the recovery period.

Phase C (14-Day repeated dose): Test article-related clinical observations were limited to soft or mucoid stools and diarrhea that were observed in a dose-related fashion for all test article-treated groups (Groups 2-5: 1.5, 15, 30, and 300 mg/kg BID, respectively). In addition, dehydration was observed in one Group 5 male. Gastrointestinal disturbances subsided after cessation of dose administration by Day 16 for Group 2 and by Day 18 in the remaining Groups 3-5 during the recovery period.

Body Weights:

Phase A (single dose): The mean initial (Day 1) and final (Day 14) body weights of the control males were 268 and 342 g, respectively. The mean initial (Day 1) and final (Day 14) body weights of the control females were 198 and 231 g, respectively. There were no significant treatment-related changes.

Phase B (5-day repeated dose): The mean initial (Day 1) and final (Day 14) body weights of the control males were 266 and 330 g, respectively. The mean initial (Day 1) and final (Day 14) body weights of the control females were 202 and 225 g, respectively. There were dose-related effects on mean body weights and body weight gains during the study. A significant reduction in mean body weight gains in Group 4 and 5 males and mean body weight losses in Group 4 (3%) and 5 females (5%) were observed during the Day 1-5 body weight interval. In addition, lower mean body weight gains were observed in Group 2 (male: 21 g vs. 27 g in control; female: 4 g vs. 7 g in control) and 3 (male: 18 g vs. 27 gm in control; female: 1 g vs. 7 g in control) males and females. By Day 19, body weights and body weight gains for all test article-treated groups were similar to the control group, indicating recovery during the 14-day recovery period.

Phase C (14-day repeated dose): The mean initial (Day 1) and final (Day 14) body weights of the control males were 269 and 333 g, respectively. The mean initial (Day 1) and final (Day 14) body weights of the control females were 201 and 223 g, respectively. Lower mean body weights were observed in the 300 mg/kg/day BID males (-10%) and in 15 (-6%) and 300 (-8%) mg/kg BID females. Mean body weight losses (-1 %) were observed at 300 mg/kg BID females on Days 1 to 8.

Reference ID: 3130340

Food Consumption:

Phase A (single dose): The mean initial (Day 1-8) and final (Day 8-14) food consumption in control males were 33 and 33 g/animal/day, respectively. The mean initial (Day 1-8) and final (day 8-14) food consumption in control females were 23 and 25 g/animal/day, respectively. There were no significant treatment-related changes.

Phase B (5-day repeated dose): The mean initial (Day 1-5) and final (Day 14-19) food consumption in control males were 31 and 31 g/animal/day, respectively. The mean initial (Day 1-5) and final (day 14-19) food consumption in control females were 21 and 22 g/animal/day, respectively. Food consumption was decreased at 30 mg/kg BID in males (87% of control) and 300 mg/kg BID doses in males (81% of control) and females (81% of control).

Phase C (14-day repeated dose): The mean initial (Day 1-8) and final (Day 8-14) food consumption in control males were 31 and 30 g/animal/day, respectively. The mean initial (Day 1-8) and final (Day 8-14) food consumption in control females were 20 and 22 g/animal/day, respectively. There were no significant treatment-related changes.

Hematology: There were no significant treatment-related changes for any Phase.

Clinical Chemistry: No significant treatment-related changes were observed for any Phase.

Urinalysis: There were no other significant treatment-related changes for any Phase.

Gross Pathology:

Phase A (single dose): Test article-related findings (abnormal mucoid contents) were observed on Day 2 in the gastrointestinal tract (jejunum, ileum, cecum, colon, large intestine and/or rectum) in all test article groups. There were no apparent test article-related findings observed during necropsy examination on Day 15 (recovery termination). The following table (from page 39 of the report) shows the gross necropsy findings.

Gross Internal Necropsy Findings for Main Study Animals - Day 2

Sex	Finding	Group 1	Group 2	Group 3	Group 4	Group 5
Males	Cecum - content abnormal	--	--	5/10	4/10	6/10
	Colon - content abnormal	--	--	2/10	--	--
	Ileum - content abnormal	--	1/10	--	--	1/10
	Ileum - diverticulum	1/10	--	--	--	--
	Kidney - dilated pelvis	--	--	2/10	--	--
	Kidney, cortex - focus	1/10	--	--	--	--
	Large Intestine - content abnormal	--	2/10	2/10	2/10	4/10
	Rectum - content abnormal	--	--	1/10	--	--
	Thymus - foci	--	--	--	--	2/10

Group 1 (0 mg/kg/dose) Group 2 (1.5 mg/kg/dose) Group 3 (15 mg/kg/dose) Group 4 (30 mg/kg/dose) Group 5 (300 mg/kg/dose)

Gross Internal Necropsy Findings for Main Study Animals - Day 2

Sex	Finding	Group 1	Group 2	Group 3	Group 4	Group 5
Females	Cecum - content abnormal	--	3/10	4/10	3/10	4/10
	Ileum - content abnormal	--	--	4/10	2/10	2/10
	Jejunum - content abnormal	--	--	--	--	1/10
	Kidney - dilated pelvis	--	1/10	--	--	--
	Large Intestine - content abnormal	--	--	4/10	4/10	3/10
	Rectum - content abnormal	--	1/10	1/10	--	--
	Thymus - discoloration	--	--	--	--	1/10
	Thymus - foci	--	--	--	1/10	--
	Ureter - distended	--	1/10	--	--	--

Group 1 (0 mg/kg/dose) Group 2 (1.5 mg/kg/dose) Group 3 (15 mg/kg/dose) Group 4 (30 mg/kg/dose) Group 5 (300 mg/kg/dose)

Gross Internal Necropsy Findings for Main Study Animals - Day 15

Sex	Finding	Group 1	Group 2	Group 3	Group 4	Group 5
Males	Epididymides - discoloration	--	--	--	1/5	--
	Kidney - dilated pelvis	--	1/5	--	--	1/5
	Kidney - discoloration	--	--	--	1/5	--
	Thymus - foci	--	--	--	1/5	--
	Thymus - discoloration	1/5	--	--	--	--
Females	Ileum - content abnormal	--	1/5	--	--	--
	Iliac Lymph Node - enlarged	--	1/5	--	--	--
	Thymus - discoloration	--	--	1/5	1/5	--
	Ureter - distended	--	1/5	--	--	--
	Urinary Bladder - thickened	--	1/5	--	--	--
	Urinary Bladder - calculi	--	1/5	--	--	--

Group 1 (0 mg/kg/dose) Group 2 (1.5 mg/kg/dose) Group 3 (15 mg/kg/dose) Group 4 (30 mg/kg/dose) Group 5 (300 mg/kg/dose)

Phase B (5-Day repeated dose): Test article-related findings (abnormal mucoid contents) were observed in the gastrointestinal tract (ileum, cecum, colon, large intestine and/or rectum) in all test article groups. There were no test article-related findings observed on Day 20 following the 14-day recovery period. Gross internal necropsy findings are summarized in the following tables (from page 52-53 of the study report).

Gross Internal Necropsy Findings for Main Study Animals - Day 6

Sex	Finding	Group 1	Group 2	Group 3	Group 4	Group 5
Males	Cecum - content abnormal	--	1/10	7/10	6/10	8/10
	Colon - content abnormal	--	--	1/10	2/10	1/10
	Ileum - content abnormal	--	--	--	1/10	3/10
	Large Intestine - content abnormal	--	--	2/10	3/10	2/10
	Lung - focus	--	--	--	1/10	--
	Spleen - raised area(s)	--	1/10	--	--	--
	Thymus - discoloration	1/10	--	--	--	--

Group 1 (0 mg/kg/dose) Group 2 (1.5 mg/kg/dose) Group 3 (15 mg/kg/dose) Group 4 (30 mg/kg/dose) Group 5 (300 mg/kg/dose)

Gross Internal Necropsy Findings for Main Study Animals - Day 6

Sex	Finding	Group 1	Group 2	Group 3	Group 4	Group 5
Females	Cecum - content abnormal	--	4/10	1/10	6/10	4/10
	Colon - content abnormal	--	--	--	1/10	1/10
	Ileum - content abnormal	--	1/10	--	1/10	2/10
	Large Intestine - content abnormal	--	1/10	7/10	4/10	6/10
	Mandibular Lymph Node - foci	1/10	--	--	--	--
	Rectum - content abnormal	--	--	--	--	1/10
	Thymus - focus	1/10	--	1/10	--	--
	Thymus - discoloration	--	--	1/10	1/10	--
	Thymus - foci	--	--	1/10	1/10	--
	Uterus - cyst(s)	1/10	--	--	--	--
	Uterus - excessive fluid contents	1/10	--	--	--	--
Group 1 (0 mg/kg/dose) Group 2 (1.5 mg/kg/dose) Group 3 (15 mg/kg/dose) Group 4 (30 mg/kg/dose) Group 5 (300 mg/kg/dose)						

Gross Internal Necropsy Findings for Main Study Animals - Day 20

Sex	Finding	Group 1	Group 2	Group 3	Group 4	Group 5
Males	Cecum - content abnormal	--	1/5	1/5	--	--
	Mandibular Lymph Node - discoloration	1/5	--	--	--	--
Females	Ovary - small	--	--	--	--	1/5
	Uterus - cyst(s)	--	--	--	--	1/5
Group 1 (0 mg/kg/dose) Group 2 (1.5 mg/kg/dose) Group 3 (15 mg/kg/dose) Group 4 (30 mg/kg/dose) Group 5 (300 mg/kg/dose)						

Phase C (14-Day repeated dose): Test article-related findings (abnormal mucoid contents) were observed on Day 15 in the gastrointestinal tract (ileum, cecum, colon, large intestine, and/or rectum) in all test article groups. After the 14-day recovery period, some portions of the gastrointestinal tract still exhibited abnormal contents. Gross necropsy findings are summarized in the following tables (from page 65-66 of the study report).

Gross Internal Necropsy Findings for Main Study Animals - Day 15

Sex	Finding	Group 1	Group 2	Group 3	Group 4	Group 5
Males	Cecum - content abnormal	--	1/10	6/10	8/10	7/10
	Colon - content abnormal	--	--	--	1/10	--
	Ileum - content abnormal	--	--	1/10	--	1/10
	Jejunum - content abnormal	--	--	--	1/10	1/10
	Large Intestine - content abnormal	--	--	--	2/10	3/10
	Prostate - small	--	--	--	--	1/10
	Seminal Vesicle - small	--	--	--	--	1/10
Group 1 (0 mg/kg/dose) Group 2 (1.5 mg/kg/day) Group 3 (15 mg/kg/dose) Group 4 (30 mg/kg/dose) Group 5 (300 mg/kg/dose)						

Gross Internal Necropsy Findings for Main Study Animals - Day 15 (Continued)

Sex	Finding	Group 1	Group 2	Group 3	Group 4	Group 5
Males	Small Intestine - content abnormal	--	--	--	--	1/10
	Thymus - small	1/10	--	--	--	--
Females	Cecum - content abnormal	--	2/10	5/10	5/10	5/10
	Colon - content abnormal	--	--	1/10	--	3/10
	Ileum - content abnormal	--	--	--	1/10	2/10
	Kidney - dilated pelvis	1/10	--	--	--	--
	Large Intestine - content abnormal	--	2/10	2/10	4/10	5/10
	Stomach, glandular - focus	--	--	--	--	1/10
	Thymus - discoloration	--	--	--	1/10	1/10
	Thymus - foci	--	1/10	--	--	--
	Thyroid - small	--	1/10	--	--	--
	Uterus - cyst(s)	--	--	--	1/10	--
Group 1 (0 mg/kg/dose) Group 2 (1.5 mg/kg/day) Group 3 (15 mg/kg/dose) Group 4 (30 mg/kg/dose) Group 5 (300 mg/kg/dose)						

Gross Internal Necropsy Findings for Main Study Animals - Day 29

Sex	Finding	Group 1	Group 2	Group 3	Group 4	Group 5
Males	Oral Cavity - incisor(s) broken	--	--	1/5	--	--
	Epididymides - nodule(s)	1/5	--	--	--	--
	Epididymides - small	--	1/5	--	--	--
	Kidney, Cortex - pitted	--	1/5	--	--	--
	Mandibular Lymph Node - foci	--	1/5	--	--	--
	Testes - small	--	1/5	--	--	--
	Thymus - foci	--	1/5	--	--	--
Females	Cecum - content abnormal	--	1/5	--	--	--
	Thymus - discoloration	--	--	--	--	1/5
Group 1 (0 mg/kg/dose) Group 2 (1.5 mg/kg/day) Group 3 (15 mg/kg/dose) Group 4 (30 mg/kg/dose) Group 5 (300 mg/kg/dose)						

Organ Weights: There were no significant treatment-related changes for any Phase.

Histopathology:

Phase A (single dose): Histopathology findings were observed in the cecum (minimal to mild submucosal edema, minimal lymphoplasmacytic infiltration, and minimal mucosal hyperplasia) and rectum (minimal to mild lymphoplasmacytic infiltration). The incidence of all changes was greater in females than males. The histopathology findings are summarized below (from page 42 of the report):

Incidence and Severity of Test Article-Related Findings in the Intestines at Terminal Euthanasia (Phase A, Day 2)

	Males					Females				
Group	1	2	3	4	5	1	2	3	4	5
Dose (mg/kg/dose)	0	1.5	15	30	300	0	1.5	15	30	300
No. of animals examined	10	10	10	10	10	10	10	10	10	10
Mucosal Hyperplasia										
Cecum	(0)	(0)	(1)	(1)	(1)	(0)	(0)	(2)	(0)	**(6)[a]**
Minimal	0	0	1	1	1	0	0	2	0	**6**
Lymphoplasmacytic Infiltration										
Cecum	(3)	(3)	(2)	(2)	(3)	(1)	(4)	(3)	**(7)**	**(9)**
Minimal	3	3	2	2	3	1	4	3	**7**	**9**
Rectum	(0)	(0)	(0)	(2)	(1)	(0)	(1)	(3)	(3)	**(7)**
Minimal	0	0	0	2	1	0	1	3	3	**6**
Mild	0	0	0	0	0	0	0	0	0	**1**
Submucosal Edema										
Cecum	(0)	(0)	(0)	(0)	(1)	(0)	(0)	**(5)**	**(7)**	**(6)**
Minimal	0	0	0	0	1	0	0	**4**	**7**	**6**
Mild	0	0	0	0	0	0	0	**1**	**0**	**0**
Rectum	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)
Minimal	0	0	0	0	0	0	0	1	0	0

[a]Dose levels considered to be test article related are in bold.

Phase B (5-Day repeated dose): Test article-related histopathological findings were observed in all levels of intestine on Day 6 (main termination). These findings were limited to mucosal hyperplasia and lymphoplasmacytic infiltration of minimal to mild severity. The incidence and severity of these findings were greater in females than males. Following the 14-day recovery period (Day 20 recovery termination), there were few histopathology findings and none of the findings were considered to be test article related. There was a low incidence of mucosal hyperplasia and lymphoplasmacytic infiltration in the various levels of intestine but there was no clear difference among treated and control groups. The histopathological findings are summarized below (from 56 of the study report).

Incidence and Severity of Test Article-Related Findings in the Intestines at Terminal Euthanasia (Phase B, Day 6)

	Males					Females				
Group	1	2	3	4	5	1	2	3	4	5
Dose (mg/kg/dose)	0	1.5	15	30	300	0	1.5	15	30	300
No. of animals examined	10	10	10	10	10	10	10	10	10	10
Mucosal Hyperplasia										
Cecum	(0)	(0)	(1)	**(5)**	**(8)**	(0)	(2)	**(5)**	**(5)**	**(3)**
Minimal	0	0	**1**	**5**	**4**	0	2	**5**	**3**	**1**
Mild	0	0	0	**0**	**4**	0	0	**0**	**2**	**2**
Colon	(0)	(0)	(0)	(1)	**(3)**	(0)	(0)	(0)	(0)	(1)
Minimal	0	0	0	**1**	**3**	0	0	0	0	1
Duodenum	(1)	(0)	(2)	**(7)**	**(9)**	(5)	(3)	**(8)**	**(7)**	**(10)**
Minimal	1	0	2	**7**	**5**	5	3	**8**	**5**	**8**
Mild	0	0	0	**0**	**4**	0	0	**0**	**2**	**2**
Ileum	(0)	(0)	(0)	(1)	**(7)**	(0)	(0)	(1)	**(5)**	**(9)**
Minimal	0	0	0	1	**5**	0	0	1	**5**	**6**
Mild	0	0	0	0	**2**	0	0	0	**0**	**3**
Jejunum	(0)	(0)	(0)	**(3)**	**(8)**	(0)	(0)	(1)	**(3)**	**(9)**
Minimal	0	0	0	**3**	**4**	0	0	**1**	**2**	**5**
Mild	0	0	0	**0**	**4**	0	0	0	**1**	**4**
Rectum	(0)	(0)	(1)	**(4)**	**(8)**	(0)	(0)	(1)	**(2)**	**(5)**
Minimal	0	0	1	**4**	**4**	0	0	**1**	**2**	**3**
Mild	0	0	0	**0**	**4**	0	0	0	**0**	**2**
Lymphoplasmacytic Infiltration										
Cecum	(1)	(2)	(0)	(2)	**(4)**	(3)	(5)	(1)	(2)	(2)
Minimal	1	2	0	2	**4**	3	5	1	2	2
Duodenum	(2)	(0)	(2)	**(6)**	**(9)**	(3)	(3)	**(8)**	**(8)**	**(10)**
Minimal	2	0	2	**6**	**7**	3	3	**8**	**7**	**10**
Mild	0	0	0	**0**	**2**	0	0	**0**	**1**	**0**
Ileum	(0)	(0)	(0)	(0)	**(8)**	(0)	(0)	(1)	**(5)**	**(8)**
Minimal	0	0	0	0	**7**	0	0	1	**5**	**8**
Mild	0	0	0	0	**1**	0	0	0	**0**	**0**
Jejunum	(0)	(0)	(0)	**(3)**	**(7)**	(1)	(0)	(1)	(0)	**(7)**
Minimal	0	0	0	**3**	**7**	1	0	1	0	**7**
Rectum	(0)	(0)	(1)	**(2)**	**(2)**	(1)	(0)	(0)	(0)	**(2)**
Minimal	0	0	1	**2**	**2**	1	0	0	0	**2**

[a]Dose levels considered to be test article related are in bold.

Phase C (14-day repeated dose): Test article-related histopathology findings were observed on Day 15 (main termination) in all levels of intestine. These findings were limited to mucosal hyperplasia and lymphoplasmacytic infiltration of minimal to mild severity. The incidence and severity of these findings were greater in females than males. Histopathology changes are shown in the following table (page 69 of the study report).

Incidence and Severity of Test Article-Related Findings in the Intestines at Terminal Euthanasia (Phase C, Day 15)

	Males					Females				
Group	1	2	3	4	5	1	2	3	4	5
Dose (mg/kg/dose)	0	1.5	15	30	300	0	1.5	15	30	300
No. of animals examined	10	10	10	10	10	10	10	10	10	10
Mucosal Hyperplasia										
Cecum	(0)	(0)	**(2)**	**(9)**	**(10)**	(0)	(0)	**(9)**	**(9)**	**(10)**
Minimal	0	0	**2**	**5**	**3**	0	0	**7**	**4**	**4**
Mild	0	0	**0**	**4**	**7**	0	0	**2**	**5**	**5**
Colon	(0)	(0)	(0)	**(2)**	**(5)**	(0)	(0)	**(2)**	**(1)**	**(3)**
Minimal	0	0	0	**2**	**4**	0	0	**2**	**1**	**3**
Mild	0	0	0	**0**	**1**	0	0	**0**	**0**	**0**
Duodenum	(1)	(1)	**(5)**	**(10)**	**(10)**	(2)	(2)	**(9)**	**(10)**	**(10)**
Minimal	1	1	**4**	**2**	**6**	2	2	**3**	**2**	**4**
Mild	0	0	**1**	**8**	**4**	0	0	**6**	**8**	**6**
Ileum	(0)	(0)	(0)	**(7)**	**(6)**	(0)	(0)	**(6)**	**(8)**	**(7)**
Minimal	0	0	0	**6**	**3**	0	0	**6**	**3**	**2**
Mild	0	0	0	**1**	**3**	0	0	**0**	**5**	**5**
Jejunum	(0)	(0)	(1)	**(8)**	**(9)**	(0)	(0)	**(7)**	**(10)**	**(9)**
Minimal	0	0	1	**6**	**5**	0	0	**7**	**8**	**6**
Mild	0	0	0	**2**	**4**	0	0	**0**	**2**	**3**
Rectum	(0)	(0)	**(2)**	**(5)**	**(8)**	(0)	(0)	**(4)**	**(9)**	**(8)**
Minimal	0	0	**2**	**3**	**3**	0	0	**4**	**5**	**5**
Mild	0	0	**0**	**2**	**5**	0	0	**0**	**4**	**3**
Lymphoplasmacytic Infiltration										
Cecum	(0)	(1)	(1)	**(4)**	**(3)**	(1)	(2)	**(3)**	**(7)**	**(7)**
Minimal	0	1	1	**3**	**3**	1	2	**2**	**7**	**6**
Mild	0	0	0	**1**	**0**	0	0	**1**	**0**	**1**
Colon	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
Minimal	1	0	0	0	0	0	0	0	0	0
Duodenum	(4)	(2)	**(6)**	**(9)**	**(9)**	(4)	(3)	**(9)**	**(10)**	**(10)**
Minimal	4	2	**4**	**1**	**5**	4	3	**5**	**3**	**5**
Mild	0	0	**2**	**8**	**4**	0	0	**4**	**7**	**5**
Ileum	(1)	(0)	(0)	**(7)**	**(7)**	(0)	(1)	**(5)**	**(7)**	**(7)**
Minimal	1	0	0	**7**	**4**	0	1	**5**	**4**	**3**
Mild	0	0	0	**0**	**3**	0	0	**0**	**3**	**4**
Jejunum	(1)	(0)	(2)	**(8)**	**(8)**	(1)	**(5)**	**(7)**	**(10)**	**(8)**
Minimal	0	0	1	**7**	**5**	1	**5**	**7**	**8**	**6**
Mild	1	0	1	**1**	**3**	0	**0**	**0**	**2**	**2**
Rectum	(1)	(0)	(1)	**(2)**	**(3)**	(0)	(0)	**(2)**	**(8)**	**(3)**
Minimal	1	0	1	**2**	**2**	0	0	**2**	**8**	**3**
Mild	0	0	0	**0**	**1**	0	0	**0**	**0**	**0**

[a]Dose levels considered to be test article related are in bold.

Summary: Sodium picosulfate administered orally twice daily at 1.5, 15, 30, and 300 mg/kg BID or 3, 30, 60 and 600 mg/kg/day for 1, 5 and 14 days produced gastrointestinal clinical signs (soft or mucoid stools and diarrhea). In addition, treatment-related lower mean body weights and lower mean body weight gains were observed in Phase B and C animals (5-day and 14-day repeated dose, respectively). Gross pathology findings included treatment-related abnormal mucoid in the portions of the gastrointestinal tract in Phase A, B and C animals. Target organs appeared to be the intestine (mucosal hyperplasia, submucosal edema, and lymphoplasmacytic infiltration) and rectum (minimal to mild lymphoplasmacytic infiltration). The incidences and severity of histopathology findings were greater in females than males. Following the 14-day recovery periods, all histopathology findings were recovered except for females in the

cecum. The NOAEL could not be determined, as treatment-related adverse effects were observed at all doses.

14-Day Oral (gavage) Toxicology Study with Sodium Picosulfate in Dogs (XHM00039)

The review of this study report is incorporated below from the pharmacology review of IND 101738 dated March 23, 2010.

Reference ID: 3130340

Study Title: 14-Day Oral (gavage) Toxicology Study with Sodium Picosulfate in Dogs

Key Study Findings:

- Animals were tested at 15, 150 and 600 mg/kg BID or 30, 300 and 1200 mg/kg/day
- There was no mortality. Clinical signs included soft stool and diarrhea at mid- and high-dose.
- There were no significant treatment-related effects on body weight and food consumption
- Apparent test article-related effects on clinical chemistry parameters included increases in globulin and total protein with corresponding decreases in A/G ratio in males and females at 300 and 1200 mg/kg/day.
- The target organ could not be identified in the absence of any significant histopathology findings.
- The NOAEL appeared to be 30 mg/kg/day

Study No.: XHM00039

Volume # Page #: 12, 1

Conducting Laboratory and Location: (b) (4)

Date of Study Initiation: July 23, 2008

Date of Study Completion: April 1, 2009

GLP Compliance: A statement of compliance was included.

QA Report: yes (X) no ( )

Drug, Lot #, and % Purity: Sodium picosulfate, 651316, 99.2%

Methods:

Doses: 0 (water), 15, 150 and 600 mg/kg BID or 30, 300 and 1200 mg/kg/day. Doses were administered twice daily 8 hours apart.

Basis of dose selection: The dose levels were selected based on results of a rising-dose with a maximum tolerated dose (MTD) phase study (b) (4). Study No. XHM00038, the report not submitted). The MTD was

1000 mg/kg/day which resulted in dehydration and was, therefore, considered too high for a 14-day repeated-dose study. The low-dose level was selected as a 10x of the intended clinical dose (10 mg drug to a 70 kg person, ~0.15 mg/kg BID). Based on this information, the high-dose level was expected to produce some toxic effects, but not excessive lethality that would prevent meaningful evaluation. The mid-dose level was expected to produce minimal to moderate toxic effects. The low-dose level was expected to produce no observable indications of toxicity.

Species/Strain: Beagle dogs

Number/Sex/Group or Time Point (Main Study): 3/sex/dose

Route, Formulation, and Volume: Oral (gavage), solution, 10 mL/kg

Satellite Groups Used for Toxicokinetics or Recovery: None

Age: 9 months

Weight: Males: 6.4-7.4 kg; Females: 6.1-8.2 kg

Study Design: the following table (from page 17 of the study report) shows the study design.

6.3. Experimental Design

The experimental design was as follows:

Experimental Design

Group No.	No. of Animals		Test Material	Dose Level (mg/kg/dose)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)
	Male	Female				
1	3	3	Reverse Osmosis Deionized Water	0	0	10
2	3	3	Sodium Picosulphate	15	1.5	10
3	3	3	Sodium Picosulphate	150	15	10
4	3	3	Sodium Picosulphate	600	60	10

Observation and Times:

Mortality: Twice daily

Clinical Signs: Twice daily

Body Weights: Weekly

Food Consumption: Weekly

Ophthalmoscopy: Day-6 and Day 10

Electrocardiography: Day-6 and Day 9

Hematology: Day -8 and at necropsy

Clinical Chemistry: Day -8 and at necropsy

Urinalysis: Day -8 and at necropsy

Gross Pathology: At necropsy

Organ Weights: The following (from page 21 of the report) organs were weighed from all animals at necropsy:

7.8.2. Organ Weights

The following organs were weighed for all animals at scheduled euthanasia:

Organ Weights

Adrenal gland[a]	Pituitary gland
Brain	Prostate gland
Epididymis[a]	Salivary gland[a]
Heart	Spleen
Kidney[a]	Testis[a]
Liver	Thymus
Lung	Thyroid gland with parathyroid gland[a]
Ovary[a]	Uterus
[a]Paired organ weight.	

Histopathology: The following (from page 22 of the study report) tissues were examined from all animals.

Tissue Collection and Preservation

Adrenal gland (paired)	Lymph node, mesenteric
Animal identification	Mammary gland
Aorta	Nerve, optic (paired)[b]
Bone, femur	Nerve, sciatic
Bone, sternum	Ovary (paired)
Bone marrow, sternum	Pancreas
Bone marrow smear[a]	Parathyroid gland[c]
Brain (cerebrum, cerebellum, brain stem, medulla)	Pituitary gland
Cervix	Prostate gland
Epididymis (paired)	Salivary gland, mandibular (paired)
Esophagus	Skeletal muscle (thigh)
Eye (paired)[b]	Skin (mammary)
Gallbladder	Spinal cord (cervical, thoracic, lumbar)
Heart	Spleen
Intestine, cecum	Stomach (cardiac, fundic, pyloric)
Intestine, colon	Testis (paired)
Intestine, duodenum	Thymus
Intestine, ileum with Peyer's patch[c]	Thyroid gland (paired)
Intestine, jejunum	Tongue
Intestine, rectum	Trachea
Kidney (paired)	Urinary bladder
Liver	Uterus
Lung	Vagina
Lymph node, mandibular	Gross lesions/masses

[a]Bone marrow smears were collected from the rib at scheduled necropsies only (for possible examination).
[b]Preserved in Davidson's fixative and then transferred to 10% neutral buffered formalin.
[c]Examined only if present in the routine section.

Toxicokinetics: None

Results:

Mortality: None

Clinical Signs: Test article-related clinical observations were limited to expected pharmacological responses of soft stools and diarrhea that were observed in a dose-related fashion at the mid and high doses.

Body Weights: The mean initial (Day 1) and final (Day 14) body weights of the control males were 7.025 and 7.077 kg, respectively. The mean initial (Day 1) and final (Day 14) body weights of the control females were 6.847 and 6.856 kg, respectively. There were no significant treatment-related changes.

Food Consumption: The mean initial (Week 1) and final (Week 2) food consumption in control males were 179 and 205 g/animal/day, respectively. The mean initial (Week 1) and final (Week 2) food consumption in control females were 186 and 211g/animal/day, respectively. There were no significant treatment-related changes.

Ophthalmoscopy: There were no test article-related ophthalmic changes.

Electrocardiography: No significant treatment-related changes were observed.

Hematology: There were no significant treatment-related changes.

Clinical Chemistry: Apparent test article-related effects on clinical chemistry parameters included increases in globulin and total protein with corresponding decreases in A/G ratio in males and females at 300 and 1200 mg/kg/day. Statistically significant differences in mean clinical chemistry parameters are presented in the following table (from page 28 of the report).

Statistically Significant Differences in Clinical Chemistry Parameters

Sex	Day	Parameter	Group	Statistically Significant Value	Concurrent Control Value	Historical Control Normalized Range
Males	15	GGT, Serum	Group 3 ↓	2.62	3.19	0.890 – 2.500
			Group 4 ↓	2.71		
		Cholesterol	Group 3 ↑	193	140	123.0 – 194.0
		Triglyceride	Group 2 ↑	69	32	28.0 – 51.0
		Globulin	Group 3 ↑	2.63	1.89	1.890 – 2.370
			Group 4 ↑	2.68		
		A/G Ratio	Group 3 ↓	1.14	1.75	1.200 – 1.650
			Group 4 ↓	1.15		
		Calcium	Group 2 ↓	9.81	10.27	9.700 – 10.950
Females	15	Total Bilirubin	Group 3 ↓	0.12	0.21	0.200 – 0.470
			Group 4 ↓	0.12		
		Total Protein	Group 4 ↑	5.93	4.96	4.820 – 5.570
		Globulin	Group 4 ↑	2.86	1.78	1.710 – 2.200
		A/G Ratio	Group 3 ↓	1.23	1.79	1.350 – 1.830
			Group 4 ↓	1.13		

Group 2 (15 mg/kg/dose) Group 3 (150 mg/kg/dose) Group 4 (600 mg/kg/dose)

Urinalysis: There were no significant treatment-related changes.

Gross Pathology: There were no significant treatment-related changes.

Organ Weights: There were no significant treatment-related changes.

Histopathology: There were no significant treatment-related changes.

Summary: In a 14-day oral toxicology study in dogs, animals were treated (twice daily, 8 hours apart) with sodium picosulfate at 15, 150 and 600 mg/kg BID or 30, 300 and 1200 mg/kg/day. The target organ could not be identified in the absence of any

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significant treatment-related histopathology findings. The NOAEL was considered as 30 mg/kg/day. The sponsor did not conduct any TK analysis and used 3 animals/sex/dose. At least 4 animals/sex/dose should have been used.

Study title: A 28-Day Toxicity Study of PicoPrep Administered by Oral Gavage to Rats with a 14-Day Recovery Period

Study no.:	XHM00052
Study report location:	Section 4.2.3.2.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	April 20, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	PicoPrep, Batch No. 010901T-2, 100%

Key Study Findings:

- There was no mortality.
- Treatment-related clinical signs included soft stool and diarrhea.
- There were treatment-related reductions in body weight and food consumption at the high dose.
- Treatment-related clinical chemistry changes included decrease in electrolytes (Na, K and Cl) at the high dose.
- Treatment-related gross pathology findings included abnormal contents in the gastrointestinal tract.
- There were no significant treatment-related histopathology changes.
- The target organs could not be identified in the absence of any significant histopathology findings.
- The NOAEL was considered as the highest tested dose of 2000 mg/kg BID.

Methods:

Doses:	230, 750, 2000 mg/kg BID*
Frequency of dosing:	BID (approximately 8 hours apart)
Route of administration:	Oral (Gavage)
Dose volume:	10 mL/kg
Formulation/Vehicle:	Deionized Water
Species/Strain:	Sprague Dawley (SD) Rats
Number/Sex/Group:	10
Age:	8 weeks
Weight:	Males: 199-228 g; Females: 157 to 190 g
Satellite groups:	Yes (9/sex/dose)
Study design:	The study design is shown in the table (from page 12 of the report) below.
Deviation from study protocol:	Protocol deviations did not affect the integrity or validity of the study from a scientific or GLP perspective.

Experimental Design for the Toxicity and Toxicokinetic Phases

Group No.	No. of Animals				Dose Material	PICOPREP (Drug Product) Dose Level[a] (mg/kg/dose)	Sodium Picosulfate Dose Level[b] (mg/kg/dose)	PICOPREP (Drug Product) Concentration[c] (mg/mL)	Dose Volume (mL/kg)
	Toxicity (Recovery)		Toxicokinetic						
	Males	Females	Males	Females					
1	10 (5)	10 (5)	3	3	RODI water	0	0	0	10
2	10 (5)	10 (5)	9	9	PICOPREP	230	0.14	23	10
3	10 (5)	10 (5)	9	9	PICOPREP	750	0.46	75	10
4	10 (5)	10[d] (5)	9	9[e]	PICOPREP	2000	1.24	200	10

[a]Doses were administered BID (approximately 8 hours apart).
[b]Based on 10 mg sodium picosulfate within 16.13 g of drug product.
[c]Maximum concentration was based on intended human drug product dose concentration of 16.13 g (1 sachet) with 150 mL of water.
[d]Group 4 female #8277 was replaced with #8347 on 04 May 2010, which was Day 1 for this replacement animal. This replacement animal was dosed for 28 days and a gross necropsy examination was performed on Day 29 (01 June 2010).
[e]Group 4 TK female #8340 was replaced with #8348 on 04 May 2010, which was Day 1 for this replacement animal. This replacement animal was dosed for 28 days and had TK samples collected on Day 28 (beginning on 31 May 2010). The Day 1 TK samples from the original female #8340 were retained as the Day 1 samples.

*: Basis of dose selection: The dose levels were selected based on the results of a 14-day oral gavage dose ranging study in rats (n=3/sex/dose) with PicoPrep (Study No. XHM00050) at 242, 484, 806 and 1075/2000 mg/kg BID (8 hours apart, the high dose was increased to 2000 mg/kg BID two days after dosing at the 1075 mg/kg BID, 10 mL/kg). All animals survived until scheduled euthanasia on Day 15. Clinical signs included soft stools and diarrhea. There were no significant treatment-related changes in hematology, or urinalysis during the study. Clinical chemistry changes included reductions in sodium values for males and females at 1075/2000 mg/kg BID. Test article-related necropsy observations were limited to abnormal content of the gastrointestinal tract at the high dose.

Observations and Results:

Mortality: Mortality was checked twice daily. There was no mortality.

Clinical Signs: Clinical observations were performed on Days -4, 1, 8, 15, 22, 28, 29 (scheduled euthanasia animals only), 35, 42, and 43 (recovery animals, prior to the initial dose on dosing days). Treatment-related clinical signs included soft stools, diarrhea, and fecal staining that were observed in a dose-related manner at 750 and 2000 mg/kg BID. These signs were not seen after cessation of treatment. In addition, hair loss was seen in females at 2000 mg/kg BID.

Body Weights: Body weights were recorded weekly. The mean Day 1 and Day 28 body weights of the control males were 249 and 402 g, respectively. The mean Day 1 and Day 28 body weights of the control females were 191 and 258 g, respectively. In males at Day 28, body weights were 102%, 102%, 96% of control at low, mid and high dose, respectively. In females at Day 28, body weights were 98%, 93%, 93% of control at low, mid and high dose, respectively.

Food Consumption: Food consumption was recorded on a weekly basis. The mean initial (Day 1-8) and final (Day 22-28) food consumption of the control males were 30 and 32 g/animal/day, respectively. The mean initial (Day 1-8) and final (Day 22-28) food consumption of the control females were 23 and 24 g/animal/day, respectively. In males, final food consumptions were 100%, 94%, and 88% of control at low, mid and high dose, respectively. In females, final food consumptions were 96%, 87%, 78% of control at low, mid and high dose, respectively.

Ophthalmoscopy: Ophthalmological examinations were performed once prior to in-life initiation (Day -4) and during the last week of dosing (Day 25/26). There were no significant treatment-related changes.

Hematology: Samples for clinical pathology and urinalysis were collected as per the following schedule (from page 21 of the report).

Samples for Clinical Pathology Evaluation

Group Nos.	Time Point	Hematology	Coagulation	Clinical Chemistry	Urinalysis
1-4[a]	Day 29	x	x	x	x
1-4	Day 43	x	x	x	x

Note: "x" = scheduled sample collection.
[a]Samples were only collected from those animals scheduled for euthanasia on Day 29.

There were no meaningful and significant treatment-related changes.

Clinical Chemistry: Test article-related clinical chemistry findings were limited to decreases in electrolytes in Group 4 males (sodium, potassium, and chloride) and

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females (sodium and chloride). These changes were considered to be related to the expected pharmacological effects of the test article (electrolyte loss due to diarrhea). There were no apparent test article-related changes in mean clinical chemistry values at termination following the 14-day recovery period, indicating recovery. Statistically significant differences in mean clinical chemistry parameters are presented in the following table (from page 35 of the report):

Sex	Day	Parameter	Group	Statistically Significant Value	Concurrent Control Value	Historical Control Normalized Range
Males	29	AST	Group 2 ↓	66	86	53.0 - 137.0
			Group 3 ↓	63		
			Group 4 ↓	72		
		GGT	Group 2 ↑	0.07	0.00	0.000 - 0.950
			Group 4 ↑	0.07		
		Glucose	Group 4 ↓	130	150	93.0 - 222.0
		Urea Nitrogen	Group 2 ↓	12	15	11.0 - 22.0
			Group 3 ↓	12		
		Calcium	Group 2 ↑	10.03	9.66	8.840 - 10.440
			Group 3 ↑	10.11		
		Phosphorus	Group 3 ↑	8.66	7.91	6.440 - 9.530
		Sodium	Group 4 ↓	141	143	141.0 - 148.0
		Potassium	Group 4 ↓	4.46	4.76	3.990 - 5.140
		Chloride	Group 4 ↓	99	102	101.0 - 108.0
	43	Urea Nitrogen	Group 2 ↓	11	15	11.0 - 21.0
Females	29	Urea Nitrogen	Group 4 ↑	18	13	12.0 - 26.0
		Creatinine	Group 4 ↑	0.29	0.26	0.180 - 0.470
		Calcium	Group 2 ↑	10.44	9.97	9.050 - 10.750
		Sodium	Group 4 ↓	139	142	140.0 - 146.0
		Potassium	Group 2 ↑	4.66	4.09	3.620 - 5.030
			Group 3 ↑	4.52		
		Chloride	Group 4 ↓	98	103	101.0 - 108.0
	43	Creatinine	Group 2 ↓	0.25	0.31	0.250 - 0.440
		Phosphorus	Group 3 ↑	7.03	6.02	4.100 - 7.830
			Group 4 ↑	7.13		
Group 2 (230/0.14 mg/kg/dose BID) Group 3 (750/0.46 mg/kg/dose BID) Group 4 (2000/1.24 mg/kg/dose BID)						

Urinalysis: Urine pH were increased at Day 29 in the high dose males (pH: 7.1, 6.9 and 8.0 at low, mid and high dose, respectively, control = 6.9) and females (pH: 6.8, 6.9 and 8.5 at low, mid and high dose, respectively, control = 6.8). Specific gravity was also

increased at Day 29 in high dose males (1.016, 1.024 and 1.031 at low, mid and high dose, respectively, control = 1.019) and high dose females (1.022, 1.017 and 1.044 at low, mid and high dose, respectively, control = 1.018).

Gross Pathology: Gross pathology was conducted at necropsy. On Day 29, test article-related findings were limited to abnormal contents in the gastrointestinal tract (cecum, colon, and rectum) at 750 and 2000 mg/kg BID in both sexes.

Organ Weights: The following (from page 23 of the report) organs were weighed.

Organ Weights

Adrenal gland[a]	Prostate gland
Brain	Salivary gland[a]
Epididymis[a]	Seminal vesicle[a]
Heart	Spleen
Kidney[a]	Testis[a]
Liver	Thymus
Lung	Thyroid gland with parathyroid gland[a]
Ovary[a]	Uterus
Pituitary gland	
[a]Paired organ weight.	

There were no significant treatment-related changes.

Histopathology: The following (from page 24 of the report) tissues were collected for histopathology.

Tissue Collection and Preservation

Adrenal gland (paired)	Mammary gland
Animal identification	Nerve, optic[b]
Aorta	Nerve, sciatic
Bone, femur	Ovary (paired)
Bone, sternum	Pancreas
Bone marrow, sternum	Parathyroid gland[c]
Bone marrow smear[a]	Pituitary gland
Brain (cerebrum, cerebellum, brain stem, medulla)	Prostate gland
Cervix	Salivary gland (paired)
Epididymis (paired)	Seminal vesicle (paired)
Esophagus	Skeletal muscle (thigh)
Eye (paired)[b]	Skin (inguinal)
Harderian gland (paired)	Spinal cord (cervical, thoracic, lumbar)
Heart	Spleen
Intestine, cecum	Stomach (nonglandular and glandular)
Intestine, colon	Testis (paired)[d]
Intestine, duodenum	Thymus
Intestine, ileum with Peyer's patch[c]	Thyroid gland (paired)
Intestine, jejunum	Tongue
Intestine, rectum	Trachea
Kidney (paired)	Urinary bladder
Liver	Uterus
Lung	Vagina
Lymph node, mandibular	Gross lesions/masses
Lymph node, mesenteric	

[a]Bone marrow smears were collected from the femur at scheduled necropsies only (for possible examination).
[b]Preserved in Davidson's fixative and then transferred to 10% neutral buffered formalin.
[c]Examined only if present in the routine section.
[d]Preserved in modified Davidson's fixative and then transferred to 10% neutral buffered formalin.

Adequate Battery: Yes.

Peer Review: Yes

Histological Findings: There were no significant treatment-related changes in the main and in the recovery animals.

Toxicokinetics: Blood samples were collected on Days 1 and 28 at 0, 0.5, 2, 6, 12 and 24 hours time points from toxicokinetic (TK) animals.

Sodium picosulfate exposure was not dose proportional and tended to be higher in males than in females. The Cmax of sodium picosulfate was reached by 2 hours post first dose administration. Accumulation of sodium picosulfate (≤ 3.82-fold) was observed in females after repeated administration of PicoPrep. Plasma concentrations of BHPM peaked as early as 0.5 hours post first dose administration. BHPM exposure was not

dose proportional on Day 28. There were no apparent gender differences in systemic exposure to BHPM and generally no drug accumulations were observed after repeated administration of PicoPrep for 28 days. Metabolite to parent compound exposure ratios increased with increasing dose level on Day 1 but not on Day 28. BHPM exposure was approximately between 7.5 and 98.7% of sodium picosulfate. The following table (from page 5 of the amended report no. 2) shows the TK parameters for sodium picosulfate.

Sodium Picosulfate (Parent)

TK parameters of sodium picosulfate are summarized below.

Summary TK Parameters of Sodium Picosulfate in Sprague Dawley Rat Plasma Following Oral Gavage Administration of PICOPREP

Day 1									
Gender	**Group No.**	**Dose Level (mg/kg BID)**	**T_{max} (h)**	**C_{max} (ng/mL)**	**$AUC_{(0-t)}$ (ng•h/mL)**	**C_{max} (nM)[a]**	**$AUC_{(0-t)}$ (nM•h/)[a]**	**C_{max}/D* (ng/mL)/ (mg/kg/dose*)**	**$AUC_{(0-t)}$/D* (ng•h/mL)/ (mg/kg/dose*)**
Males	2	230	2	2.29	9.45	4.59	18.9	0.0100	0.0411
	3	750	0.5	7.98	26.8	16.0	53.6	0.0106	0.0357
	4	2000	0.5	20.6	92.1	41.2	184	0.0103	0.0460
Females	2	230	2	0.503	1.87	1.01	3.75	0.00219	0.00813
	3	750	0.5	5.03	14.4	10.1	28.8	0.00671	0.0192
	4	2000	2	3.62	33.2	7.25	66.6	0.00181	0.0166
Day 28									
Gender	**Group No.**	**Dose Level (mg/kg BID)**	**T_{max} (h)**	**C_{max} (ng/mL)**	**$AUC_{(0-t)}$ (ng•h/mL)**	**C_{max} (nM)[a]**	**$AUC_{(0-t)}$ (nM•h/)[a]**	**C_{max}/D* (ng/mL)/ (mg/kg/dose*)**	**$AUC_{(0-t)}$/D* (ng•h/mL)/ (mg/kg/dose*)**
Males	2	230	2	0.962	7.83	1.93	15.7	0.00418	0.0340
	3	750	0.5	4.99	44.4	9.99	88.9	0.00665	0.0592
	4	2000	0.5	14.2	156	28.4	313	0.00708	0.0782
Females	2	230	0.5	1.10	4.33	2.21	8.67	0.00479	0.0188
	3	750	0.5	5.59	17.4	11.2	34.9	0.00746	0.0232
	4	2000	2	13.8	80.2	27.7	161	0.00691	0.0401

* Doses were administered twice daily (approximately 8 hours apart). Indicated dose levels (mg/kg/dose) were used for dose normalization.

[a] Molecular Weight of Sodium Picosulfate = 499.4 g/mol.

The following table (from page 6 of the amended report no. 2) shows the TK parameters for BHPM.

Summary TK Parameters of BHPM in Sprague Dawley Rat Plasma
Following Oral Gavage Administration of PICOPREP

Day 1									
Gender	Group No.	Dose Level (mg/kg BID)	T_{max} (h)	C_{max} (ng/mL)	$AUC_{(0-t)}$ (ng•h/mL)	C_{max} (nM)[a]	$AUC_{(0-t)}$ (nM•h/)[a]	C_{max}/D* (ng/mL)/ (mg/kg/dose*)	$AUC_{(0-t)}$/D* (ng•h/mL)/ (mg/kg/dose*)
Males	2	230	NR	NR	NR	NR	NR	-	-
	3	750	12	0.333	5.61	1.20	20.0	0.000444	0.00748
	4	2000	12	1.54	23.5	5.56	84.6	0.000771	0.0117
Females	2	230	NR	NR	NR	NR	NR	-	-
	3	750	24	0.642	ANR	2.32	ANR	0.000856	-
	4	2000	24	1.51	11.5	5.46	41.4	0.000757	0.00574
Day 28									
Gender	Group No.	Dose Level (mg/kg BID)	T_{max} (h)	C_{max} (ng/mL)	$AUC_{(0-t)}$ (ng•h/mL)	C_{max} (nM)[a]	$AUC_{(0-t)}$ (nM•h/)[a]	C_{max}/D* (ng/mL)/ (mg/kg/dose*)	$AUC_{(0-t)}$/D* (ng•h/mL)/ (mg/kg/dose*)
Males	2	230	12	0.178	1.09	0.641	3.93	0.000773	0.00474
	3	750	6	0.553	9.23	1.99	33.3	0.000737	0.0123
	4	2000	0.5	1.40	22.6	5.06	81.5	0.000702	0.0113
Females	2	230	12	0.109	1.39	0.392	5.00	0.000473	0.00603
	3	750	24	0.481	9.54	1.73	34.4	0.000641	0.0127
	4	2000	12	1.31	25.1	4.71	90.3	0.000653	0.0125

* Doses were administered twice daily (approximately 8 hours apart). Indicated dose levels (mg/kg/dose) were used for dose normalization.

[a] Molecular Weight of BHPM = 277.3 g/mol.

ANR: AUC not reportable because the number of consecutive quantifiable plasma concentrations post dose was less than 3.

NR: Not reportable due to all concentration values are < LLOQ.

- Not calculated

Dosing Formulation Analysis: Samples were analyzed for sodium picosulfate and citric acid concentrations. Overall, samples were within acceptable limits of ±15% error. Homogeneity analysis results of Day 1 samples were within the acceptable range of ≤5% for sodium picosulfate and citric acid.

Sodium picosulfate: Stability of formulations ranging from 20 to 200 mg/mL concentration of PicoPrep (0.012- 0.12 mg/mL of sodium picosulfate) and storage conditions (room temperature, light protection) was confirmed for 15 days.

Citric acid: Stability of formulations ranging from 20 to 200 mg/mL concentration of PicoPrep (14.8 -148.8 mg/mL of citric acid, protected from light) and storage conditions (room temperature, protected from light) was confirmed for 15 days.

Summary: In a 28-day oral gavage study with PicoPrep in rats, animals were administered 230, 750 and 2000 mg/kg BID doses. The target organ could not be identified in the absence of any significant histopathology findings. The NOAEL was considered as 2000 mg/kg BID.

Study title: A 28-Day Toxicity Study of PicoPrep Administered by Oral Gavage to Dogs with a 14-Day Recovery Period

Study no.:	XHM00053
Study report location:	Section 4.2.3.2.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 21, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	PicoPrep, Batch No. 010901T-2, 100%

Key Study Findings:

- There was no mortality
- Treatment-related clinical signs included soft stool and diarrhea.
- The target organ could not be identified in the absence of significant histopathology findings.
- The NOAEL was considered to be 1000 mg/kg BID.

Methods:

Doses:	230, 500, 1000 mg/kg BID*
Frequency of dosing:	BID (approximately 8 hours apart)
Route of administration:	Oral (Gavage)
Dose volume:	10 mL/kg
Formulation/Vehicle:	Deionized water
Species/Strain:	Beagle Dogs
Number/Sex/Group:	10
Age:	6 Months
Weight:	Males: 6.4-7.9 kg; Females: 5.9 – 8.2 kg
Satellite groups:	Yes (5/sex/dose)
Study design:	The study design is shown in the table (from page 20 of the report) below.
Deviation from study protocol:	Protocol deviations did not affect the integrity or validity of the study from a scientific or GLP perspective.

*: Basis of dose selection: The dose levels were selected based on the results of a 14-day oral gavage dose ranging study in dogs (n=3/sex/dose) with PicoPrep (Study No. XHM00051) at 242, 484, 806 and 1075 mg/kg BID (8 hours apart, 10 mL/kg). All animals survived until scheduled euthanasia on Day 15. Treatment-related clinical signs included soft stools and diarrhea at 806 and 1075 mg/kg BID doses. There were no significant treatment-related changes in hematology, clinical chemistry or urinalysis parameters. Test article-related necropsy observations were limited to abnormal content

Reference ID: 3130340

of the gastrointestinal tract. Based on the results of this study, the high dose was selected as 1000 mg/kg BID for the current 28-day study in dogs.

Experimental Design

Group No.	No. of Toxicity (Recovery) Animals		Test Material	PICOPREP (Drug Product) Dose Level[a] (mg/kg/dose)	Sodium Picosulfate Dose Level[b] (mg/kg/dose)	PICOPREP (Drug Product) Concentration[c] (mg/mL)	Dose Volume[a] (mL/kg/dose)
	Male	Female					
1	3 (2)	3 (2)	Reverse Osmosis Deionized Water	0	0	0	10
2	3[d] (2)	3 (2)	PICOPREP	230	0.14	23	10
3	3 (2)	3 (2)	PICOPREP	500	0.30	50	10
4	3 (2)	3 (2)	PICOPREP	1000	0.61	100	10

[a]Doses were administered BID (approximately 8 hours apart).
[b]Based on 10 mg of sodium picosulfate within 16.13 g of drug product.
[c]Maximum concentration was based on intended human drug product dose concentration of 16.13 g (1 sachet) with 150 mL of water.
[d]Group 2 male #D4140 was replaced with male #D4154. Dosing for male #D4154 began on 04 June 2010 and this dog was euthanized on 02 July 2010.

Observations and Results:

Mortality: Mortality was checked twice daily. There was no mortality.

Clinical Signs: Clinical observations were performed once prior to treatment (Day -1**)** and weekly during the treatment and recovery periods (Days **1,** 8, 15, 22, 28, 35, and 42). Treatment-related clinical signs included soft stools and diarrhea that were observed in a dose-related manner. These signs subsided after cessation of the dose administration.

Body Weights: Body weights were recorded on a weekly basis. The mean initial (Day 1) and final (Day 28) body weights of the control males were 7.11 and 8.21 kg, respectively. The mean initial (Day 1) and final (Day 28) body weights of the control females were 6.41 and 7.27 kg, respectively. There were no significant treatment-related effects.

Food Consumption: Food consumption was recorded on daily basis. The mean initial (Week 1) and final (Week 5) food consumption of the control males were 330 and 335 g/animal/day, respectively. The mean initial (Day 1-8) and final (Day 22-28) food consumption of the control females were 310 and 324 g/animal/day, respectively. There were no significant treatment-related effects.

Ophthalmoscopy: Ophthalmological examinations were performed prior to in-life initiation (Day -4) and during the last week of the treatment period (Day 27). There were no significant treatment-related effects.

Electrocardiography (ECG): Electrocardiographic measurements were obtained from all animals using leads I, II, III, aVR, aVL, and aVF. The ECG measurements were obtained once prior to in-life initiation (Day -2) and during the last week of dosing (Day 27). A single atrial premature depolarization was noted in two dogs (one in Group 1 and one in Group 4) on Study Day -2 and in six dogs (one in Group 1, one in Group 2, two in Group 3, and two in Group 4) on Study Day 27. This rhythm change was stated to occur occasionally in normal dogs and was not related to test article dosing as it was also seen in control dogs and there was no clear dose-response. No ventricular premature depolarizations were noted throughout the study. A left axis deviation was noted occasionally in some dogs. This axis deviation was stated to occur occasionally in normal dogs and was not related to test article dosing. There were no statistically significant changes in heart rate (HR), RR interval, PR interval, QRS duration, QT interval, or QTc throughout the study. There were no other significant treatment-related changes.

Hematology: Samples were collected for clinical pathology (hematology, clinical chemistry, and urinalysis) as per the following table (from page 22 of the report).

Samples for Clinical Pathology Evaluation

Group Nos.	Study Day	Hematology	Coagulation	Clinical Chemistry	Urinalysis
All animals	Pretest	x	x	x	x[a]
1-4	Day 29	x	x	x	x[b, c]
1-4	Day 43	x	x	x	x[b, c]

Note: "x" = scheduled sample collection.
[a]Collected by cage pan drainage.
[b]Collected by cystocentesis at gross necropsy.
[c]Urine samples were collected from toxicity animals only on Day 29 and from recovery animals only on Day 43.

There were no meaningful significant treatment-related changes.

Clinical Chemistry: There were no meaningful significant treatment-related changes.

Urinalysis: There were no meaningful significant treatment-related changes.

Gross Pathology: Gross pathology was conducted at scheduled necropsy. On Day 29, test article-related findings were limited to abnormal contents in the gastrointestinal tract (cecum, and colon as shown in the following table (from page 34 of the report).

Gross (Internal) Necropsy Findings for Main Study Animals

Sex	Day	Finding	Group 1	Group 2	Group 3	Group 4
Males	29	Cecum – abnormal content	--	--	1/3	1/3
		Colon – abnormal content	--	1/3	1/3	2/3
		Pituitary – cyst	--	1/3	--	1/3
		Rectum – abnormal content	--	--	1/3	2/3
		Spleen – area pale	--	1/3	--	--
Females	29	Cecum – abnormal content	1/3	--	--	1/3
		Colon – abnormal content	1/3	--	--	1/3
		Pituitary – cyst	--	--	--	1/3
		Subcutaneous skin – nodule	1/3	--	--	--
Group 1 (0 mg/kg/dose BID PICOPREP) Group 2 (230 mg/kg/dose BID PICOPREP) Group 3 (500 mg/kg/dose BID PICOPREP) Group 4 (1000 mg/kg/dose BID PICOPREP)						

Gross (Internal) Necropsy Findings for Recovery Animals

Sex	Day	Finding	Group 1	Group 2	Group 3	Group 4
Males	43	Kidney – mass	--	--	--	1/2
		Rectum – abnormal content	--	--	1/2	--
Females	43	Ileum – area dark	1/2	--	--	--
		Lung – small	--	--	1/2	--
		Lung – foci dark	--	--	1/2	--
Group 1 (0 mg/kg/dose BID PICOPREP) Group 2 (230 mg/kg/dose BID PICOPREP) Group 3 (500 mg/kg/dose BID PICOPREP) Group 4 (1000 mg/kg/dose BID PICOPREP)						

Organ Weights: The following (from page 25 of the report) organs were weighed.

Organ Weights

Adrenal gland[a]	Pituitary gland
Brain	Prostate gland
Epididymis[a]	Salivary gland[a]
Heart	Spleen
Kidney[a]	Testis[a]
Liver	Thymus
Lung	Thyroid gland with parathyroid gland[a]
Ovary[a]	Uterus
[a]Paired organ weight.	

There were no meaningful significant treatment-related changes.

Histopathology: The following table (from page 26 of the report) shows the list of tissues for histopathology.

Tissue Collection and Preservation

Adrenal gland (paired)	Lymph node, mesenteric
Animal identification	Mammary gland
Aorta	Nerve, optic (paired)[b]
Bone, femur	Nerve, sciatic
Bone, sternum	Ovary (paired)
Bone marrow, sternum	Pancreas
Bone marrow smear[a]	Parathyroid gland[c]
Brain (cerebrum, cerebellum, brain stem, medulla)	Pituitary gland
Cervix	Prostate gland
Epididymis (paired)	Salivary gland, mandibular (paired)
Esophagus	Skeletal muscle (thigh)
Eye (paired)[b]	Skin (inguinal)
Gallbladder	Spinal cord (cervical, thoracic, lumbar)
Heart	Spleen
Intestine, cecum	Stomach (cardiac, fundic, pyloric)
Intestine, colon	Testis (paired)[d]
Intestine, duodenum	Thymus
Intestine, ileum with Peyer's patch[c]	Thyroid gland (paired)
Intestine, jejunum	Tongue
Intestine, rectum	Trachea
Kidney (paired)	Urinary bladder
Lacrimal gland (paired)	Uterus
Liver	Vagina
Lung	Gross lesions/masses
Lymph node, mandibular	

[a]Bone marrow smears were collected from the rib at scheduled necropsies only (for possible examination).
[b]Preserved in Davidson's fixative and then transferred to 10% neutral buffered formalin.
[c]Examined only if present in the routine section.
[d]Preserved in modified Davidson's fixative and then transferred to 10% neutral buffered formalin.

Adequate Battery: Yes.

Peer Review: Yes

Histological Findings: There were no significant treatment-related microscopic changes in the main and in the recovery animals.

Toxicokinetics: Blood samples were collected for TK analysis on Days 1 and 28 as shown in the following table (from page 23 of the report).

TK Sample Collection Schedule

Group No.	No. of Males/Females	Sample Collection Time Points (Hours Post-Dose) on Days 1 and 28					
		0 hr[a]	0.5 hr	2 hr	6 hr	12 hr	24 hr
1	5/5	x	x	x	x	x	x
2	5/5	x	x	x	x	x	x
3	5/5	x	x	x	x	x	x
4	5/5	x	x	x	x	x	x

Note: "x" = scheduled sample collection.
[a]Samples collected prior to dosing on Days 1 and 28.

Sodium Picosulfate: The maximum plasma concentration (Cmax) of sodium picosulfate was generally reached by 12 or 24 hours post first dose. The daily exposure, as defined by Cmax and AUC_{0-t}, increased with increasing dose level in a dose proportional manner on Days 1 and 28. The mean exposure increased between 3 to 5-fold after 28 days of dosing, indicating accumulation after repeated administration of PicoPrep. Exposure to sodium picosulfate was similar among males and females. TK parameters (sex combined) are presented in the following table (from page 43 of the TK report).

Table 2.1 Toxicokinetic Parameters of Sodium Picosulfate in Beagle Dog Plasma Following Oral Gavage Administration of PICOPREP

Day 1 (Males)

Group No.	Dose Level (mg/kg/dose*)	Animal No.	Tmax [a] (h)	Cmax (ng/mL)	Cmax (nM) [c]	AUC(0-t) (ng•h/mL)	AUC(0-t) (nM•h) [c]	Cmax/D* (ng/mL)/ (mg/kg/dose*)	AUC(0-t)/D* (ng•h/mL)/ (mg/kg/dose*)
2	230	4134	12	82.3	165	1502	3008	0.358	6.53
		4136	24	76.0	152	1453	2909	0.330	6.32
		4140	12	68.7	138	1291	2585	0.299	5.61
		4147	24	91.2	183	1654	3313	0.397	7.19
		4150	12	60.0	120	1165	2334	0.261	5.07
		4154	12	60.6	121	1014	2031	0.263	4.41
		Mean [b]	12	73.1	146	1347	2697	0.318	5.85
		SD		12.4	24.8	235	471	0.0539	1.02

Day 1 (Females)

Group No.	Dose Level (mg/kg/dose*)	Animal No.	Tmax [a] (h)	Cmax (ng/mL)	Cmax (nM) [c]	AUC(0-t) (ng•h/mL)	AUC(0-t) (nM•h) [c]	Cmax/D* (ng/mL)/ (mg/kg/dose*)	AUC(0-t)/D* (ng•h/mL)/ (mg/kg/dose*)
2	230	4158	24	71.6	143	1197	2397	0.311	5.20
		4161	24	89.5	179	1553	3110	0.389	6.75
		4162	12	99.2	199	1798	3600	0.431	7.82
		4164	12	60.8	122	1046	2094	0.264	4.55
		4176	24	34.5	69.1	ANR	ANR	0.150	-
		Mean [b]	24	71.1	142	1399	2800	0.309	6.08
		SD		25.4	50.8	341	683	0.110	1.48
	Sex Combined	Mean [b]	12	72.2	145	1367	2738	0.314	5.95
		SD		18.3	36.7	265	530	0.0796	1.15

* Doses were administered twice daily (approximately 8 hours apart). Indicated dose levels (mg/kg/dose) were used for dose normalization.

a Time is post first dose administration.

b Median value reported for Tmax.

c Molecular weight of Sodium Picosulfate = 499.4 g/mol.

ANR AUC not reportable because the number of consecutive quantifiable plasma concentrations post dose was less than 3.

\- Not calculated.

BHPM: Plasma concentrations of BHPM peaked as early as 0.5 hours post first dose and the Cmax was generally maintained for up to 12 hours. BHPM exposure appeared to be proportional to the dose levels of sodium picosulfate and was similar among females and males. In females, accumulation of BHPM was observed after repeated administration of PicoPrep, where the AUC_{0-t} on Day 28 was up to 2.6-fold higher than

that of Day 1. BHPM exposure was less than 2% of sodium picosulfate exposure. The following table shows the mean TK parameters for BHPM (from page 10 of the TK report).

Text Table 5
Summary Mean TK Parameters of BHPM in Beagle Dog Plasma
Following Oral Gavage Administration of PICOPREP

Day 1					
Gender	**Group No.**	**Dose Level (mg/kg BID)**	**Tmax (h)**	**Cmax (ng/mL)**	**AUC(0-t) (ng•h/mL)**
Males	2	230	2	0.348	-
	3	500	2	0.786	4.00
	4	1000	2	0.976	6.62
Females	2	230	2	0.382	-
	3	500	2	0.806	4.25
	4	1000	2	1.56	8.76
Day 28					
Gender	**Group No.**	**Dose Level (mg/kg BID)**	**Tmax (h)**	**Cmax (ng/mL)**	**AUC(0-t) (ng•h/mL)**
Males	2	230	7	0.131	-
	3	500	12	0.517	5.01
	4	1000	2	1.15	10.1
Females	2	230	6	2.55	21.3
	3	500	2	1.01	11.1
	4	1000	2	1.60	17.7

Median value reported for Tmax.
- Not calculated.

Dosing Formulation Analysis: Samples were analyzed for sodium picosulfate and citric acid concentrations. Overall, samples were within acceptable limits of ±15% error on Day 1 and Day 22. Homogeneity analysis results of Day 1 samples were within the acceptable range of ≤5% for sodium picosulfate and citric acid.

Sodium picosulfate: Stability of formulations ranging from 20 to 200 mg/mL concentration of PicoPrep (0.012- 0.12 mg/mL of sodium picosulfate) and storage conditions (room temperature, protected from light) was confirmed for 15 days.

Citric acid: Stability of formulations ranging from 20 to 200 mg/mL concentration of PicoPrep (14.8 -148.8 mg/mL of citric acid, protected from light) and storage conditions (room temperature, protected from light) was confirmed for 15 days.

Summary: In a 28-day oral gavage study with PicoPrep in dogs, animals were administered at 230, 500 and 1000 mg/kg BID doses. The target organ could not be identified in the absence of any significant histopathology findings. The NOAEL was considered as 1000 mg/kg BID.

7 Genetic Toxicology

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

Ames test with Sodium Picosulfate (Report No. 783137)

The review of this study report is incorporated below from the pharmacology review of original IND 101738 dated March 23, 2010.

Study Title: Ames test with Sodium Picosulfate

Key Findings: Negative

Study No.: 783137

Volume #, Page #: Vol. 14, 1
Conducting Laboratory and Location: (b) (4)
Date of Study Initiation: July 6, 2007
Date of Study Completion: October 12, 2007
GLP Compliance: A statement of compliance was included.
QA Reports: yes (X) no ( )
Drug, Lot #, and % Purity: Sodium picosulfate, Lot 601316, 100%

Methods: Two independent tests were conducted in triplicate. The first test was conducted by the direct plate method, while the second was conducted by the pre-incubation method.

Strains/species/cell line: *Salmonella typhimurium* and *Escherichia coli*

Doses used in definitive study: 17, 50, 167, 500, 1667 and 5000 µg/plate

Basis of dose selection: Cytotoxicity

Negative controls: Water

Positive controls: The following (from page 17 of the report) positive controls were used.

6.8.2 Positive Controls

The following positive control materials were plated in triplicate:

With S9 mix:

2-Aminoanthracene (2AAN): 2 µg per plate with *S. typhimurium* TA 1535 and TA 1537, 0.5 µg per plate with *S. typhimurium* TA 98 and TA 100 and 20 µg per plate with *E. coli* WP2*uvr*A

Without S9 mix:

Sodium azide (NaN_3): 1 µg per plate with TA 1535 and TA 100
N-Ethyl-N-nitro-N-nitrosoguanidine (ENNG): 2 µg per plate with *E. coli* WP2*uvr*A
2-Nitrofluorene (2-NF): 1 µg per plate with TA 98
9-Aminoacridine (9-AA): 80 µg per plate with TA 1537

Incubation and sampling times: 37^0C for 2-3 days

Results

Study validity: The study was considered valid as the study met the criteria for a valid assay as follows.

- At least 2 of the 3 vehicle control plates were within the following ranges: *S. typhimurium* TA 1535, 4-30; TA 100, 60-200; TA 1537, 1-30; TA 98, 10-60 and *E. coli* WP2uvrA, 1-60.
- There were at least 2-fold increases over the mean vehicle control values in at least 2 of the 3 positive control plates for each strain and activation state (in the case of TA 100, at least 1.5-fold was required).

Criteria for positive response: The following are the criteria for a positive response.

- For *S. typhimurium* strains TA 1535, TA 1537, and TA 98 and for E. coli WP2uvrA, at least a doubling of the mean concurrent vehicle control value
- For *S. typhimurium* strain TA 100, a 1.5-fold increase over the control value

Study outcome: Negative. The following tables (page 28-29 of the report) show the results of the confirmatory test (pre-incubation).

Table 3 Second Mutation Assay (Pre-incubation)

Without metabolic activation

Strain	Compound	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts
TA 1535	**Sodium**	17 µg	*20.7*	*3.2*	*1.0*	22, 17, 23
	Picosulphate	50 µg	*18.3*	*4.5*	*0.9*	14, 23, 18
		167 µg	*18.0*	*5.6*	*0.9*	24, 13, 17
		500 µg	*18.7*	*6.4*	*0.9*	16, 26, 14
		1667 µg	*23.3*	*4.5*	*1.2*	23, 28, 19
		5000 µg	*18.0*	*5.0*	*0.9*	13, 18, 23
	Water	-	*20.0*	*7.0*	-	15, 28, 17
TA 1537	**Sodium**	17 µg	*10.0*	*3.6*	*1.2*	11, 13, 6
	Picosulphate	50 µg	*12.7*	*1.5*	*1.5*	14, 13, 11
		167 µg	*5.3*	*0.6*	*0.6*	5, 6, 5
		500 µg	*16.3*	*4.9*	*1.9*	22, 13, 14
		1667 µg	*11.7*	*1.2*	*1.3*	11, 11, 13
		5000 µg	*10.0*	*4.0*	*1.2*	14, 10, 6
	Water	-	*8.7*	*5.5*	-	15, 6, 5
TA 98	**Sodium**	17 µg	*24.0*	*4.4*	*1.0*	27, 19, 26
	Picosulphate	50 µg	*25.7*	*5.5*	*1.0*	22, 23, 32
		167 µg	*23.3*	*10.1*	*0.9*	34, 14, 22
		500 µg	*24.3*	*7.1*	*1.0*	18, 32, 23
		1667 µg	*23.0*	*10.6*	*0.9*	11, 27, 31
		5000 µg	*15.7*	*4.9*	*0.6*	19, 10, 18
	Water	-	*24.7*	*4.2*	-	26, 28, 20
TA 100	**Sodium**	17 µg	*116.7*	*13.6*	*1.1*	112, 106, 132
	Picosulphate	50 µg	*101.0*	*15.6*	*0.9*	92, 119, 92
		167 µg	*110.3*	*13.4*	*1.0*	116, 95, 120
		500 µg	*102.0*	*21.2*	*1.0*	78, 110, 118
		1667 µg	*117.0*	*11.3*	*1.1*	130, 110, 111
		5000 µg	*120.7*	*9.0*	*1.1*	130, 112, 120
	Water	-	*107.0*	*10.1*	-	98, 118, 105
WP2uvrA	**Sodium**	17 µg	*9.0*	*5.3*	*0.8*	11, 3, 13
	Picosulphate	50 µg	*10.7*	*4.9*	*1.0*	14, 13, 5
		167 µg	*13.3*	*2.1*	*1.3*	14, 11, 15
		500 µg	*9.7*	*4.2*	*0.9*	11, 13, 5
		1667 µg	*15.7*	*4.2*	*1.5*	17, 19, 11
		5000 µg	*8.7*	*5.0*	*0.8*	14, 8, 4
	Water	-	*10.7*	*2.5*	-	11, 13, 8

Table 3 (continued) **Second Mutation Assay (Pre-incubation)**

Without metabolic activation

Strain	Compound	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts
TA 1535	**NaN_3**	1 µg	*450.3*	*56.1*	*22.5*	515, 422, 414
TA 1537	**9AA**	80 µg	*4585.7*	*578.4*	*529.1*	5248, 4180, 4329
TA 98	**2NF**	1 µg	*1023.3*	*68.4*	*41.5*	1071, 945, 1054
TA 100	**NaN_3**	1 µg	*1039.3*	*23.2*	*9.7*	1013, 1048, 1057
WP2uvrA	**ENNG**	2 µg	*185.3*	*30.3*	*17.4*	220, 172, 164

Key to Positive Controls

NaN_3	Sodium Azide
9AA	9-Aminoacridine
2NF	2-Nitrofluorene
ENNG	N-Ethyl-N-Nitro-N-nitrosoguanadine

7.2 In Vitro Assays in Mammalian Cells

The review of this study report is incorporated below from the pharmacology review of original IND 101738 dated March 23, 2010.

Study Title: Mouse Lymphoma Assay with Sodium Picosulfate

Key Findings: Negative

Study No.: 783142

Volume #, Page #: Vol. 14, 37
Conducting Laboratory and Location: [redacted] (b) (4)
Date of Study Initiation: July 6, 2007
Date of Study Completion: November 23, 2007
GLP Compliance: A statement of compliance was included.
QA Reports: yes (X) no ( )
Drug, Lot #, and % Purity: Sodium picosulfate, Lot 601316, 100%

Methods:

Cell line: L5178Y mouse lymphoma $TK^{+/-}$ cell line

Doses used in definitive study: 625, 1250, 2500 and 5000 µg/mL

Basis of dose selection: Cytotoxicity

Negative controls: Water

Positive controls: The positive control materials used in the absence of S9 mix (4 h exposure period) were: 250 µg/mL ethyl methanesulphonate (EMS), a large colony inducer; and 10 µg/mL methyl methanesulphonate (MMS), which usually induces greater numbers of small colonies. When performing an experiment using the extended, 24 h exposure period, these concentrations were reduced to 150 µg EMS/mL and 5 µg

MMS/mL. In the presence of S9 mix, 3-methylcholanthrene (3-MC), a large and small colony inducer, was used at a concentration of 2.5 µg/mL. EMS and 3-MC were dissolved in DMSO, while MMS was dissolved in water.

Incubation and sampling times: 4 hr and 24 hr exposure at 37^{0}C. The following table (from page 10 of the report) shows the study design.

Four independent mutation experiments were conducted as follows:

Experiment No.	Presence or absence of S9	Treatment time (hours)	Final concentrations† (µg/mL)
1	Absence	4	625, 1250, 2500, 5000‡
2	Presence	4	625, 1250, 2500, 5000
3	Absence	24	625, 1250, 2500, 5000
4	Presence	4	625, 1250, 2500, 5000

† Concentrations taken through to final assessment
‡ 5000 µg/mL represents the predetermined maximum concentration

Results:

Study validity: The study was considered valid as it met the criteria for a valid assay.

Criteria for positive response: An experiment was considered positive if one or more concentrations were biologically significant and there was a significant linear trend. An experiment may also have been classed as positive in the absence of a linear trend if there was mitigating evidence. This may have been, for example, the presence of a similar level of toxicity at all concentrations assessed. In such a case, the confirmatory experiment would have been expected to assess concentrations covering different levels of toxicity, to establish a linear trend.

Study outcome: Negative. The following tables (from page 36-39 of the report) show the results.

Table 4 **Mutation Test in the Absence of S9 Mix (4 h Exposure) Summary of Means of Data (Assay 1)**

Chemical	Concentration (µg/mL)	Relative Total Growth %	Mutant Fraction (x 10^{-6})	IMF (Induced Mutant Fraction x10^{-6})	Ratio of Small to Large Colonies	Statistical Comparison
Water	(100 µl added)	100	101	-	1.22	-
EMS	250	71	588	488	0.46	*
MMS	10	36	882	782	3.45	*
Sodium Picosulphate	312.5	NPS	NPS	-	-	-
	625	121	76	-	2.75	-
	1250	110	98	-	1.09	-
	2500	132	69	-	0.81	-
	5000	125	101	1	1.10	-

IMF = Mutant fraction of treatment minus mutant fraction of vehicle control group
* = Significant difference in log mutant fraction compared with vehicle control (P<0.05)
Test for linear trend of mutant fraction with concentration of Sodium Picosulphate = not reported – slope negative
NPS = Not Plated - Surplus

Table 5 **Mutation Test in the Presence of S9 Mix (4 h Exposure) Summary of Means of Data (Assay 2)**

Chemical	Concentration (µg/mL)	Relative Total Growth %	Mutant Fraction (x 10^{-6})	IMF (Induced Mutant Fraction x10^{-6})	Ratio of Small to Large Colonies	Statistical Comparison
Water	(100 µl added)	100	109	-	1.22	-
3-MC	2.5	59	924	815	1.57	*
Sodium Picosulphate	312.5	NPS	NPS	-	-	-
	625	93	116	7	1.94	-
	1250	97	80	-	1.73	-
	2500	100	88	-	0.89	-
	5000	80	84	-	1.38	-

IMF = Mutant fraction of treatment minus mutant fraction of vehicle control group
* = Significant difference in log mutant fraction compared with vehicle control (P<0.05)
Test for linear trend of mutant fraction with concentration of Sodium Picosulphate = not reported – slope negative
NPS = Not Plated - Surplus

Table 6 Mutation Test in the Absence of S9 Mix (24 h Exposure) Summary of Means of Data (Assay 3)

Chemical	Concentration (µg/mL)	Relative Total Growth %	Mutant Fraction (x 10^{-6})	IMF (Induced Mutant Fraction x10^{-6})	Ratio of Small to Large Colonies	Statistical Comparison
Water	(200 µl added)	100	63	-	0.60	-
EMS	150	24	1886	1822	0.29	*
MMS	5	24	1189	1125	1.70	*
Sodium Picosulphate	312.5	NPS	NPS	-	-	-
	625	78	81	18	0.90	-
	1250	70	47	-	0.69	-
	2500	64	34	-	1.29	-
	5000	57	48	-	1.07	-

IMF = Mutant fraction of treatment minus mutant fraction of vehicle control group
* = Significant difference in log mutant fraction compared with vehicle control ($P<0.05$)
Test for linear trend of mutant fraction with concentration of Sodium Picosulphate = not reported – slope negative
NPS = Not Plated - Surplus

Table 7 Mutation Test in the Presence of S9 Mix (4 h Exposure) Summary of Means of Data (Assay 4)

Chemical	Concentration (µg/mL)	Relative Total Growth %	Mutant Fraction (x 10^{-6})	IMF (Induced Mutant Fraction x10^{-6})	Ratio of Small to Large Colonies	Statistical Comparison
Water	(100 µl added)	100	58	-	0.66	-
3-MC	2.5	39	944	886	1.24	*
Sodium Picosulphate	312.5	NPS	NPS	-	-	-
	625	97	60	2	0.84	-
	1250	94	44	-	0.38	-
	2500	78	46	-	1.46	-
	5000	61	54	-	0.71	-

IMF = Mutant fraction of treatment minus mutant fraction of vehicle control group
* = Significant difference in log mutant fraction compared with vehicle control ($P<0.05$)
Test for linear trend of mutant fraction with concentration of Sodium Picosulphate = not reported – slope negative
NPS = Not Plated - Surplus

7.3 In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

The review of this study report is incorporated below from the pharmacology review of original IND 101738 dated March 23, 2010.

Study Title: *In Vivo* Mouse Micronucleus Test with Sodium Picosulfate by Intravenous Route

Key Findings: Negative

Study No.: 783158

Volume #, Page #: Vol. 14, 105
Conducting Laboratory and Location: (b) (4)
Date of Study Initiation: September 5, 2007
Date of Study Completion: January 28, 2008
GLP Compliance: A statement of compliance was included.
QA Reports: yes (X) no ( )
Drug, Lot #, and % Purity: Sodium picosulfate, Lot 601316, 100%

Methods: In the micronucleus test, groups of CD-1 mice (male: 34-40 g; female: 22-28 g, age 6-7 weeks) were treated at 0 hr and 24 hr *via* the intravenous route with the test article at 400, 800 and 1600 mg/kg (10 mL/kg). Bone marrow samples were taken 48 h after the initial 0 h dose. Two control groups of CD-1 mice were treated intravenously with either the vehicle (10 mL/kg) water, or the positive control agent, 50 mg/kg, IV of cyclophosphamide. At least two thousand (2000)-polychromatic erythrocytes (PCE) per animal were scored for micronuclei and the frequency of micro nucleated cells (MN-PCE) was determined. The PCE/NCE (normochromatic erythrocyte) ratio, a measure of any induced systemic toxicity, was determined by counting a minimum total of 1000 erythrocytes (PCE + NCE) per marrow preparation.

Species: CD-1 mice

Doses used in definitive study: 400, 800 and 1600 mg/kg

Basis of dose selection: A toxicity study was conducted to establish a suitable dose range for the micronucleus experiment. The toxicity study was conducted using 6 groups of male and female CD-1 mice, dosed intravenously at 0 h + 24 h with sodium picosulfate as follows (from page 17 of the report). The mice were observed for clinical signs or mortality at frequent intervals (1 min, 0.5 h, 1 h, 2 h and 4 h post dosing), then twice daily until the end of the observation period. Surviving animals were subsequently sacrificed.

Phase No.	Group No.	No. of Mice	Dose Level (mg/kg/day)
1	1	1M + 1F	500
	2	1M + 1F	1000
2	3	1M + 1F	1500
	4	1M + 1F	2000
3	5	3M + 3F	1600
	6	3M + 3F	1800

In the above toxicity study, mortality was observed at 2000 and 1800 mg/kg doses. The accompanying clinical signs were convulsions, tremors, hunched, labored breathing, staggering, subdued behavior, agitated, piloerection and dark tail. Based on the findings of the toxicity study, the maximum dose of sodium picosulfate was considered to be around 1600 mg /kg/day.

Negative controls: Water

Positive controls: Cyclophosphamide 50 mg/kg, IV

Incubation and sampling times: In the micronucleus test, groups of CD-1 mice were dosed intravenously at 0 h and 24 h with test or control materials, then marrow samples taken 24 hr later as shown in the following table (from page 17 of the report) shows the study design.

Dose Group	Daily Test Dose	Treatment and Number of Mice		
		Dosing (h)	Sampling (h)	No. of Mice
Vehicle Control	10 mL water for injection/kg	0 + 24	48	5M + 5F
Low Dose	400 mg Sodium picosulphate/kg	0 + 24	48	5M
Mid Dose	800 mg Sodium picosulphate/kg	0 + 24	48	5M
High Dose	1600 mg Sodium picosulphate/kg	0 + 24	48	10M +10F
Positive Control	50 mg Cyclophosphamide/kg	0 + 24	48	5M

Results:

Study validity: The study was considered valid as it met criteria for a valid assay.

Criteria for positive response: The results were considered positive if an increase in the number of micronucleated polychromatic erythrocytes (M-PCE) was obtained for one or more of the test item treated dose groups (i.e., an increase >10% over the expected

historical control ranges for a group of animals). The increase observed should be biologically relevant and statistically significant relative to concurrent and historical control frequencies for MN-PCE and/or MN-NCE induction.

Study outcome: Negative. The following table (from page 27 of the report) shows the results.

Table 3 Summary of Assessment Data

Treatment	Dose (h)	Sex	No. of Rats Scored	Erythrocytes				
				Normochromatic Cells (NCE)	Polychromatic Cells (PCE)			PCE/NCE
				No. of MN-NCE	PCE Analysed	No. of MN-PCE	% MN-PCE	Mean ± S.D.
10 mL Water for injection kg/day	0 + 24	M	5	5	10009	0	0.00	0.76 ± 0.13
		F	5	3	10008	5	0.05	0.82 ± 0.12
		M/F	10	8	20017	5	0.02	0.79 ± 0.12
400 mg Sodium picosulphatekg/day	0 + 24	M	5	6	10010	3	0.03	0.70 ± 0.09
800 mg Sodium picosulphate /kg/day	0 + 24	M	5	2	10004	0	0.00	0.82 ± 0.12
1600 mg Sodium picosulphate /kg/day	0 + 24	M	5	6	10008	1	0.01	0.82 ± 0.18
		F	5	3	10006	4	0.04	0.83 ± 0.11
		M/F	10	9	20014	5	0.02	0.83 ± 0.14
50 mg Cyclophosphamide/kg/day	0 + 24	M	5	53α	10004	128	1.28Φ	0.50 ± 0.06

PCE = Polychromatic erythrocytes
MN-PCE = Micronucleated PCE
NCE = Normochromatic erythrocytes
MN-NCE = Micronucleated NCE
Φ = Positive response in PCE
α = Evident response in NCE

7.4 Other Genetic Toxicity Studies

None

8 Carcinogenicity

None

9 Reproductive and Developmental Toxicology

The applicant did not conduct reproductive toxicology studies with sodium picosulfate. However, the applicant provided literature references regarding the reproductive toxicity

of sodium picosulfate, which was reviewed under IND 10738. The following is incorporated from the pharmacology review of IND 101738 dated March 20, 2010.

Reproductive Toxicology: Teratology studies [Nishimura, M., Kast, A. and Tsunenari, Y. l976. Oyo Yakuri (Pharmacometrics) 12, 67-78; Nishimura, M., Kast, A. and Tsunenari, Y. 1977. Iyakuhin Kenkyu, 8, 366-396] have been performed in rats at oral dosage levels of up to 10,000 mg/kg/day (GD 9 to GD 14), and in rabbits at dosage levels

up to 1,000 mg/kg/day (GD 8 to GD 16). In rats, there was lower maternal weight gain at ≥ 100 mg/kg/day. However this effect was seen at 1,000 mg/kg/day in rabbits. In rats, embryofetal toxicity (lower fetal weight and increased resorptions) was observed at 1,000 and 10,000 mg/kg/day, and at 1,000 mg/kg/day in rabbits. There was no evidence of teratogenicity at any dosage level, in both species. The rat study included a postnatal phase, which revealed low birth weights and smaller litter size following earlier exposure to the two high dosage levels of 1,000 and 10,000 mg/kg/day. Subsequent growth, development, behavior and reproductive function were unaffected.

In oral fertility studies (Nishimura, M., Kast, A. and Tsunenari, Y. 1977. Iyakuhin Kenkyu, 8, 366-396) in rats and rabbits, there was no significant treatment-related effect of sodium picosulfate at dosage levels up to 100 mg/kg/day on mating performance and fertility. However, when the treatment of pregnant females continued up until day 7 of pregnancy, and when their fetuses were assessed at day 21 of pregnancy, there was a slight reduction in litter size at 10 and 100 mg/kg/day, with a slight increase in fetal weight.

In a peri- and postnatal study (Nishimura, M., Kast, A. and Tsunenari, Y. 1977. Iyakuhin Kenkyu, 8, 366-396) in rats, animals were treated at 1, 10, and 100 mg/kg/day of sodium picosulfate. There was a slight reduction of weight gain at 100 mg/kg/day on GD 17. Number of dead pups at birth at 100 mg/kg/day was increased, and body weight gain of offsprings was slightly decreased at 10 and 100 mg/kg/day compared to control. Post-weaning growth, development, behavior and reproductive function were unaffected by the treatment.

9.1 Fertility and Early Embryonic Development

Study title: Oral (Gavage) Fertility and General Reproduction Toxicity Study of PicoPrep in Rats

Study no.:	XHM00048
Study report location:	4.2.3.5.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 29, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	PicoPrep, 010901T-2, 100%

Key Study Findings:

- In an oral fertility and early embryonic development to implantation study in rats, animals were treated with PicoPrep at 230, 750 and 2000 mg/kg BID.
- PicoPrep did not cause any significant adverse effect on fertility and early embryonic development in male and female rats.
- The NOAEL for effects on fertility and reproductive performance was considered as 2000 mg/kg BID.

Methods: PioPrep or water (control) were administered via oral gavage twice daily (BID) to male rats beginning 28 days before cohabitation (maximum 16 days) and continuing through the day before euthanasia. Female rats were administered the test article and/or the control article twice daily (BID, 8 hours apart) beginning 15 days before cohabitation (maximum 16 days) and continuing through gestation day 7 (DG 7). The test and control articles were administered at dosage levels of 0 (Control Article), 230, 750 and 2000 mg/kg BID (PicoPrep) at a dosage volume of 10 mL/kg. Male rats were euthanized after the completion of the cohabitation period; reproductive organs were weighed and retained and sperm evaluations were conducted. Female rats were euthanized on DG 13, Caesarean-sectioned and examined for gross lesions. The number and distribution of corpora lutea, implantation sites, viable and nonviable embryos were recorded.

Doses:	230, 750 and 2000 mg/kg BID*
Frequency of dosing:	BID (8 hours apart)
Dose volume:	10 mL/kg
Route of administration:	Oral (Gavage)
Formulation/Vehicle:	Deionized water
Species/Strain:	SD Rats
Number/Sex/Group:	25/sex/group
Satellite groups:	None
Study design:	The study design is shown below (from page 24 of the study report)
Deviation from study protocol:	There were no deviations that affected the outcome or interpretation of this study. All deviations that occurred in this study were incidental in nature as they were documentation or recording errors, were minimal excursions from specific data collection endpoints (e.g., test article administration) or minor procedural errors that deviated from the original intent of the experimental design. These types of deviations from the protocol did not seem to have any significant impact on the study outcome or interpretation of the data.

*: Basis of dose selection: The doses were selected based on the results of a dose ranging developmental toxicity study (XHM00044) in rats.

Reference ID: 3130340

In this study, mated female rats were administered 0 (Control), 230, 750, 1500 and 2000 mg/kg PicoPrep twice daily (BID), 8 hours apart, on DGs 7 through 17 at a dosage volume of 10 mL/kg. All female rats survived to scheduled euthanasia. Clinical signs included ungroomed coat and soft or liquid feces at 750, 1500 and 2000 mg/kg BID, and mucoid feces at 2000 mg/kg BID. Body weight losses or reductions in body weight gain, as well as reductions in food consumption values, were observed at 750, 1500 and 2000 mg/kg BID at various intervals within the dosage period. Mean body weight gains were 105%, 95%, 84% and 65% of the control group value in the 230, 750, 1500 and 2000 mg/kg BID groups, respectively. During the entire dosage period (DGs 7 through 18) absolute (g/day) food consumption values were 105%, 94%, 92% and 87% of the control group value and relative (g/kg/day) food consumption values were 104%, 96%, 95% and 90% of the control group value at 230, 750, 1500 and 2000 mg/kg BID, respectively. No Caesarean-sectioning or litter parameters on DG 21 were affected by the treatment with PicoPrep. There were no significant treatment-related fetal gross external alterations. Based on the results of this study, dosage levels of 0 (Control Article), 230, 750 and 2000 mg/kg BID PicoPrep were selected for the current study (XHM00048). The lowest dosage level of PicoPrep, 230 mg/kg BID, approximates the clinical dose (a single administration of PicoPrep in a 70 kg human patient is 16.13 g, which includes 10 mg sodium picosulfate, resulting in a dose of 0.14 mg/kg sodium picosulfate). The mid-dose, 750 mg/kg BID, represents a >3-fold exposure margin. The high dose, 2000 mg/kg BID, represents >8-fold exposure margin, relative to the lowest dosage level, and was selected to demonstrate maternal toxicity, as evidenced by the body weight changes and reductions in food consumption observed in the dose ranging study (Protocol XHM00044).

Dosage Group	Number of Rats Per Sex	PICOPREP (Drug Product) Dosage (mg/kg/dose)[a]	Sodium Picosulphate Dosage (mg/kg/dose)[b]	PICOPREP (Drug Product) Concentration (mg/mL)	Dosage Volume (mL/kg/dose)
I	25	0 (Control Article)	0 (Control Article)	0	10
II	25	230	0.14	23	10
III	25	750	0.45	75	10
IV	25	2000	1.2	200	10

a. Doses were administered BID 8 hours apart (±30 minutes).
b. Based on 10 mg of sodium picosulphate within 16.13 g of PICOPREP.

Observations and Results:

Mortality: Mortality was observed twice daily. Two female rats (8284 and 8299) at 2000 mg/kg BID were found dead during GD 2 and 1, respectively. Based on the necropsy observations in these female rats, these mortalities were attributed to intubation and handling errors, respectively. One female rat (8292) at 2000 mg/kg BID was found dead on DG 8. A definitive cause of death could not be determined for this female rat. Clinical signs in this female rat were limited to soft stool. Necropsy examination revealed an

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extra lung lobe, but no findings indicative of a cause of death. All other F0 generation female rats survived until scheduled euthanasia.

Clinical Signs: Clinical signs were observed twice daily. In males, treatment-related clinical signs included abnormal feces (soft or liquid feces, mucoid feces, discolored feces/light brown) at all doses. These signs were increased at higher doses. In females, clinical signs at 750 and 2000 mg/kg BID included abnormal feces, ungroomed coat, and urine-stained abnormal fur.

Body Weight: Body weights were recorded on a weekly basis. The mean initial (Day 1) and final (Day 49) body weights of control males were 363.3 and 514.3 g, respectively. The mean initial (Day1) and final (Day 14) body weight (premating) of control females were 250.6 and 261.2 g, respectively. The mean initial gestational (Day 0) and final (Day 10) body weight of control females were 265.1 and 311.7 g, respectively. In males, mean body weight gain was decreased at low (95% of control, control = 151 g), mid (85% of control) and high (85% of control) doses from Day 1-49. In females, the mean initial (Day 0) and final (Day 13) body weights were 265 and 329 g, respectively. In females, mean body weight gain was decreased at low (78% of control,), mid (15% of control) and high (88% of control) doses from Days 1-15 compared to control (control weight gain = 12.1 g). Overall, there was a reduction in body weight gain when compared to control.

Food Consumption: Food consumption was recorded on a weekly basis. The mean initial (Days 1-8) and final (Days 43-50) food consumption for control males were 70.7 and 58.7 g/kg/day, respectively. The mean initial (Days 1-8) and final (Days 8-15) food consumption (pre-mating period) for control females were 76.0 and 74.4 g/animal/day, respectively. The mean initial (Days 0-7) and final (Days 8-13) food consumption (gestational period) for control females were 80.1 and 85.3 g/animal/day, respectively. Treatment-related reductions in food consumption were observed during the precohabitation period in both sexes at 750 and 2000 mg/kg BID doses. In females, the food consumption was not significantly altered during the gestation period.

Toxicokinetics: Not conducted

Dosing Formulation Analysis: In each of the three assays (i.e., sodium picosulfate, citrate/citric acid and magnesium), samples from the first, mid-point, and last days of formulation preparation met acceptance criteria for concentration (i.e., the difference between the actual mean value and the targeted concentration was ≤ 15%) and homogeneity (i.e., the relative standard deviation [RSD] for the formulation, calculated as the RSD for the grand mean of the average values for top, middle and bottom locations, was ≤ 5%).

Necropsy: After completion of the cohabitation period, all male rats were euthanized, and a gross necropsy of the thoracic, abdominal and pelvic viscera was performed. Reproductive organs were weighed and retained for possible histopathological evaluation and sperm evaluations (concentration and motility) were conducted. The

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following organs were individually weighed: right testis, left testis, left epididymis (whole and cauda), right epididymis, seminal vesicles (with and without fluid) and prostate.

There were no necropsy observations in the male rats attributed to treatment with the test article. It is to be mentioned here that one male rat (8136) at 230 mg/kg BID had a mass on the left cauda epididymis; the cut surface revealed a tan, firm material. Another male rat (8144) at 230 mg/kg BID had flaccid testes and a small left testis, epididymis, and cauda epididymis. Slight dilation in the left kidney, a calculus in the right kidney, dilated ureters, calculi in the urinary bladder and thickened bladder walls were observed in one male rat (8172) in the 750 mg/kg BID group. These were not considered as treatment-related in the absence of these findings at higher doses. In females, there were no significant treatment-related necropsy findings.

Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.): All surviving female rats were euthanized on DG 13, Caesarean-sectioned and a gross necropsy of the thoracic, abdominal and pelvic viscera was performed. Uteri were dissected and examined for implantation sites, number and distribution of corpora lutea and viable and nonviable embryos. Placentae were examined for size, color and shape.

In males, there were no significant treatment-related effects on mating and fertility index and sperm parameters. In females, the number of estrous stages per 14 days was comparable among the four dosage groups before the start of dosage administration and during the precohabitation period and did not significantly differ. All mating and fertility parameters (numbers of days in cohabitation, rats that mated, the fertility index) were unaffected by the treatment. No Caesarean-sectioning parameters were affected by the treatment with PicoPrep. The litter averages for corpora lutea, implantations, preimplantation loss, viable and nonviable embryos and postimplantation loss were comparable among the four dosage groups and did not significantly differ. No dam had a litter consisting of only nonviable embryos. All placentae appeared normal. The following table (from page 127 of the report) shows the Caesarean-sectioning data.

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TABLE B12 (PAGE 1): CAESAREAN-SECTIONING AND LITTER OBSERVATIONS (CAESAREAN-DELIVERED EMBRYOS) - SUMMARY - FEMALE RATS

DOSAGE GROUP		I	II	III	IV
PICOPREP DRUG PRODUCT (MG/KG/DOSE)a		0 (CONTROL ARTICLE)	230	750	2000
SODIUM PICOSULPHATE (MG/KG/DOSE)a,b		0 (CONTROL ARTICLE)	0.14	0.45	1.2
RATS TESTED	N	25	25	25	25
PREGNANT	N(%)	24(96.0)	24(96.0)	23(92.0)	23(92.0)
FOUND DEAD	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.3)
RATS PREGNANT AND CAESAREAN-SECTIONED ON DAY 13 OF GESTATION	N	24c	24	23	22
CORPORA LUTEA	MEAN±S.D.	16.4 ± 2.2	16.0 ± 2.1	15.4 ± 2.0	15.4 ± 1.4
IMPLANTATIONS	MEAN±S.D.	15.5 ± 1.9	15.4 ± 2.1	15.0 ± 2.0	15.0 ± 1.2
% PREIMPLANTATION LOSS	MEAN±S.D.	5.0 ± 7.2	3.6 ± 4.5	2.2 ± 3.1	2.5 ± 4.1
VIABLE EMBRYOS	N	357	354	325	319
	MEAN±S.D.	14.9 ± 2.0	14.8 ± 1.8	14.1 ± 2.4	14.5 ± 1.6
NONVIABLE EMBRYOS	N	15	15	21	11
	MEAN±S.D.	0.6 ± 0.6	0.6 ± 0.8	0.9 ± 1.3	0.5 ± 0.7
% POSTIMPLANTATION LOSS	MEAN±S.D.	4.1 ± 4.0	3.8 ± 4.7	6.3 ± 9.2	3.5 ± 4.7
DAMS WITH ANY NONVIABLE EMBRYOS	N(%)	14(58.3)	11(45.8)	11(47.8)	9(40.9)
DAMS WITH ALL NONVIABLE EMBRYOS	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
DAMS WITH VIABLE EMBRYOS	N(%)	24(100.0)	24(100.0)	23(100.0)	22(100.0)
% NONVIABLE EMBRYOS/LITTER	MEAN±S.D.	4.1 ± 4.0	3.8 ± 4.7	6.3 ± 9.2	3.5 ± 4.7

% PREIMPLANTATION LOSS = [(NUMBER OF CORPORA LUTEA - NUMBER OF IMPLANTATIONS) / NUMBER OF CORPORA LUTEA] x 100
% POSTIMPLANTATION LOSS = [(NUMBER OF IMPLANTATIONS - NUMBER OF VIABLE EMBRYOS) / NUMBER OF IMPLANTATIONS] x 100
a. Dosage occurred twice daily (BID) approximately 8 hours ± 30 minutes apart on day 1 of study through day 7 of gestation.
b. Based on 10 mg of sodium picosulphate within 16.13 g of drug product.
c. Includes values for dam 8225, which did not have a confirmed mating date.

Summary: In an oral fertility and early embryonic development to implantation study (Segment I) in rats, animals were treated with PicoPrep at 230, 750 and 2000 mg/kg BID. There were no significant treatment-related effects on fertility and reproductive performance in both sexes. The NOAEL for effects on fertility and reproductive performance was considered as 2000 mg/kg BID.

9.2 Embryonic Fetal Development

Study title: Oral (Gavage) Embryo-Fetal Developmental Study with PicoPrep in Rats

Study no.:	XHM00045
Study report location:	EDR 4.2.3.5.2.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 2, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	PicoPrep, Lot 010901T-2, 100%

Key Study Findings:

- In a Segment II oral embryofetal development study in rats, pregnant female SD rats were treated with PicoPrep at 230, 750 and 2000 mg/kg BID doses.

- There were treatment-related reductions in body weight gain and food consumption at mid and high doses.
- Treatment-related clinical signs included soft feces and dehydration and ungroomed coat at mid and high doses.
- There were no significant treatment-related effects on any intrauterine or C-section parameters.
- There no significant treatment-related gross fetal external, visceral or skeletal changes.
- PicoPrep was not teratogenic in this study.

Methods: In this study, pregnant female rats were randomly assigned to four dosage groups (n = 25/group). PicoPrep or the control article (water) was administered via oral gavage (10 mL/kg) twice daily (8 hours apart) on days 7 through 17 of gestation (DGs 7 through 17) at dosage levels of 0 (water), 230, 750 and 2000 mg/kg BID. Rats were euthanized on DG 21, Caesarean-sectioned and examined for gross lesions. The number and distribution of corpora lutea, implantation sites, and live and dead fetuses were recorded.

Doses:	0, 230, 750 and 2000 mg/kg BID*
Frequency of dosing:	Daily
Dose volume:	10 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Deionized water
Species/Strain:	SD rats
Number/Sex/Group:	25/group
Satellite groups:	None
Study design:	The study design is shown below (from page 21 of the report)
Deviation from study protocol:	The protocol deviations did not seem to have any significant impact on the study outcome or interpretation of the data.

*: Rationale for Dose selection: Doses were selected based on the results of a dosage-range developmental study (XHM00044) in rats, which was discussed before.

The study design is shown below.

Dosage Group	Number of Rats	PICOPREP (Drug Product) Dosage (mg/kg/dose)[a]	Sodium Picosulphate Dosage (mg/kg/dose)[b]	PICOPREP (Drug Product) Concentration (mg/mL)	Dosage Volume (mL/kg/dose)	Assigned Rat Numbers
I	25	0 (Control Article)	0 (Control Article)	0	10	7101 - 7125
II	25	230	0.14	23	10	7126 - 7150
III	25	750	0.45	75	10	7151 - 7175
IV	25	2000	1.2	200	10	7176 - 7200

a. Doses were administered BID 8 hours apart (±30 minutes).
b. Based on 10 mg of sodium picosulphate within 16.13 g of PICOPREP.

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Observations and Results:

Mortality: Rats were observed for viability at least twice each day. There were no mortalities.

Clinical Signs: Rats were observed for clinical signs twice each day. Treatment-related clinical signs at 750 and 2000 mg/kg BID included abnormal feces, mild dehydration, and ungroomed coat.

Body Weight: Body weights were recorded twice during the acclimation period, on DG 0 and daily during the dosage and post-treatment periods. The mean initial (Day 0) and final (Day 20) body weights of control animals were 226.8 and 376.9 g, respectively. At Day 20, maternal body weights were 99.2%, 95.5% and 95.7% of control at low, mid and high doses, respectively. During GD 7-21, mean body weight gain was reduced at low (94% of control gain), mid (87% of control gain) and high (88% of control gain) doses when compared to control weight gain (132.7 g). Overall, maternal body weight and body weight gain were reduced by treatment.

Food Consumption: Food consumption values were recorded on DGs 0, 7, 10, 12, 15, 18 and 21. The mean initial (Days 0-7) and final (Days 18-21) food consumptions in control animals were 20.3 and 22.5 g/animal/day, respectively. Mean food consumptions during Days 7-21 were 97%, 88% and 88% of control at low, mid and high dose, respectively.

Toxicokinetics: Not conducted

Dosing Formulation Analysis: In each of the three assays (i.e., sodium picosulfate, citrate/citric acid and magnesium), samples from the first and last days of formulation preparation met acceptance criteria for concentration (i.e., the difference between the actual mean value and the targeted concentration was ≤ 15%) and homogeneity (i.e., the relative standard deviation [RSD] for the formulation, calculated as the RSD for the grand mean of the average values for top, middle and bottom locations, was ≤ 5%).

Necropsy: There were no significant treatment-related effects.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.): Caesarean-sectioning or litter parameters were not affected by the treatment. The litter averages for corpora lutea, implantations, litter sizes, live fetuses, early and late resorptions, fetal body weights and percent resorbed conceptuses were comparable among the four dosage groups and did not significantly differ. No dam had a litter consisting of only resorbed conceptuses, and there were no dead fetuses. All placentae appeared normal. The following tables (from pages 46 and 47 of the report) show the Cesarean section data.

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PROTOCOL XHM00045: ORAL (GAVAGE) EMBRYO-FETAL DEVELOPMENTAL TOXICITY STUDY OF PICOPREP IN RATS

TABLE 7 (PAGE 1): CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY

DOSAGE GROUP		I	II	III	IV
PICOPREP DRUG PRODUCT (MG/KG/DOSE)a		0 (CONTROL ARTICLE)	230	750	2000
SODIUM PICOSULPHATE (MG/KG/DOSE)a,b		0 (CONTROL ARTICLE)	0.14	0.45	1.2
RATS TESTED	N	25	25	25	25
PREGNANT	N(%)	24(96.0)	22(88.0)	24(96.0)	25(100.0)
RATS PREGNANT AND CAESAREAN-SECTIONED ON DAY 21 OF GESTATION	N	24	22	24	25
CORPORA LUTEA	MEAN±S.D.	15.0 ± 2.3	15.4 ± 1.9	14.6 ± 1.6	14.6 ± 2.0
IMPLANTATIONS	MEAN±S.D.	14.3 ± 1.9	14.6 ± 1.2	14.3 ± 1.6	14.2 ± 2.1
% PREIMPLANTATION LOSS	MEAN±S.D.	3.8 ± 5.6	4.2 ± 8.5	1.7 ± 3.0	2.9 ± 6.7
LITTER SIZES	MEAN±S.D.	13.8 ± 1.8	14.1 ± 1.2	13.8 ± 1.7	13.5 ± 1.9
LIVE FETUSES	N	331	310	332	337
	MEAN±S.D.	13.8 ± 1.8	14.1 ± 1.2	13.8 ± 1.7	13.5 ± 1.9
DEAD FETUSES	N	0	0	0	0
RESORPTIONS	MEAN±S.D.	0.5 ± 0.8	0.5 ± 0.7	0.5 ± 0.8	0.7 ± 0.8
EARLY RESORPTIONS	N	12	11	12	16
	MEAN±S.D.	0.5 ± 0.8	0.5 ± 0.6	0.5 ± 0.8	0.6 ± 0.8
LATE RESORPTIONS	N	1	1	0	1
	MEAN±S.D.	0.0 ± 0.2	0.0 ± 0.2	0.0 ± 0.0	0.0 ± 0.2
% POSTIMPLANTATION LOSS	MEAN±S.D.	3.5 ± 5.1	3.6 ± 4.3	3.5 ± 5.4	4.6 ± 5.5
DAMS WITH ANY RESORPTIONS	N(%)	9(37.5)	10(45.4)	8(33.3)	12(48.0)
DAMS WITH ALL CONCEPTUSES RESORBED	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
DAMS WITH VIABLE FETUSES	N(%)	24(100.0)	22(100.0)	24(100.0)	25(100.0)
PLACENTAE APPEARED NORMAL	N(%)	24(100.0)	22(100.0)	24(100.0)	25(100.0)

% PREIMPLANTATION LOSS = [(NUMBER OF CORPORA LUTEA - NUMBER OF IMPLANTATIONS) / NUMBER OF CORPORA LUTEA] x 100
% POSTIMPLANTATION LOSS = [(NUMBER OF IMPLANTATIONS - NUMBER OF LIVE FETUSES) / NUMBER OF IMPLANTATIONS] x 100
a. Dosage occurred twice daily (BID) approximately 8 hours ± 30 minutes apart on days 7 through 17 of gestation.
b. Based on 10 mg of sodium picosulphate within 16.13 g of drug product.

PROTOCOL XHM00045: ORAL (GAVAGE) EMBRYO-FETAL DEVELOPMENTAL TOXICITY STUDY OF PICOPREP IN RATS

TABLE 8 (PAGE 1): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - SUMMARY

DOSAGE GROUP		I	II	III	IV
PICOPREP DRUG PRODUCT (MG/KG/DOSE)a		0 (CONTROL ARTICLE)	230	750	2000
SODIUM PICOSULPHATE (MG/KG/DOSE)a,b		0 (CONTROL ARTICLE)	0.14	0.45	1.2
LITTERS WITH ONE OR MORE LIVE FETUSES	N	24	22	24	25
IMPLANTATIONS	MEAN±S.D.	14.3 ± 1.9	14.6 ± 1.2	14.3 ± 1.6	14.2 ± 2.1
LIVE FETUSES	N	331	310	332	337
	MEAN±S.D.	13.8 ± 1.8	14.1 ± 1.2	13.8 ± 1.7	13.5 ± 1.9
% LIVE MALE FETUSES/LITTER	MEAN±S.D.	42.6 ± 9.8	53.4 ± 11.4**	49.4 ± 9.6	51.4 ± 14.9*
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN±S.D.	5.40 ± 0.40	5.33 ± 0.26	5.36 ± 0.29	5.48 ± 0.27
MALE FETUSES	MEAN±S.D.	5.55 ± 0.40	5.48 ± 0.29	5.50 ± 0.28	5.61 ± 0.32
FEMALE FETUSES	MEAN±S.D.	5.30 ± 0.40	5.16 ± 0.26	5.22 ± 0.32	5.34 ± 0.29
% RESORBED CONCEPTUSES/LITTER	MEAN±S.D.	3.5 ± 5.1	3.6 ± 4.3	3.5 ± 5.4	4.6 ± 5.5

a. Dosage occurred twice daily (BID) approximately 8 hours ± 30 minutes apart on days 7 through 17 of gestation.
b. Based on 10 mg of sodium picosulphate within 16.13 g of drug product.
* Significantly different from the control group value ($p \leq 0.05$).
** Significantly different from the control group value ($p \leq 0.01$).

Offspring (Malformations, Variations, etc.): There were no significant treatment-related gross fetal external, skeletal or visceral malformations . A cervical rib at the 7th cervical vertebra, was seen in 0, 1, 3 and 6 fetuses at 0, 230, 750 and 2000 mg/kg BID, respectively. The fetal incidences for this alteration were significantly increased at 750 and 2000 mg/kg BID groups, in comparison with the fetal incidence in the control article group. The litter incidences for this variation were 0, 1, 2 and 5 at 0, 230, 750 and 2000 mg/kg BID, respectively. Although there was no statistical significance for the litter incidence, however, the litter incidences appeared to be dose-related. Both the fetal and litter incidences were higher than the respective historical control ranges (litter incidence: 0.0-12.0%; fetal incidence: 0.0-1.7%). These alterations were considered a common variation in this strain of rat (Khera KS, 1981, Common Fetal Aberrations and their Teratologic Significance: a review, Fund Appl Toxicol,1:13-8). All fetal alterations that were seen were considered unrelated to treatment for the following reasons: 1) The litter incidence did not reflect a dosage-related pattern of effect; 2) the litter incidence and the fetal incidence were within the range of historical control data for the testing facility; 3) the fetal alteration occurred in a non-dosage-related manner; 4) the fetal alteration was considered a common variation in this strain of rat; and/or 5) the fetal alteration was considered a reversible delay in ossification. The following Table 10 (from page 49 of the report) shows the fetal gross external alterations.

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PROTOCOL XHM00045: ORAL (GAVAGE) EMBRYO-FETAL DEVELOPMENTAL TOXICITY STUDY OF PICOPREP IN RATS

TABLE 10 (PAGE 1): FETAL GROSS EXTERNAL ALTERATIONS - CAESAREAN-DELIVERED LIVE FETUSES (DAY 21 OF GESTATION) - SUMMARY

DOSAGE GROUP		I	II	III	IV
PICOPREP DRUG PRODUCT (MG/KG/DOSE)a		0 (CONTROL ARTICLE)	230	750	2000
SODIUM PICOSULPHATE (MG/KG/DOSE)a,b		0 (CONTROL ARTICLE)	0.14	0.45	1.2
LITTERS EVALUATED	N	24	22	24	25
FETUSES EVALUATED	N	331	310	332	337
LIVE	N	331	310	332	337
EYE(S): BULGE(S) DEPRESSED					
LITTER INCIDENCE	N(%)	0(0.0)	1(4.5)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.3)	0(0.0)	0(0.0)

a. Dosage occurred twice daily (BID) approximately 8 hours ± 30 minutes apart on days 7 through 17 of gestation.
b. Based on 10 mg of sodium picosulphate within 16.13 g of drug product.

The following Table 11 (from page 50 of the report) shows fetal visceral alterations.

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PROTOCOL XHM00045: ORAL (GAVAGE) EMBRYO-FETAL DEVELOPMENTAL TOXICITY STUDY OF PICOPREP IN RATS

TABLE 11 (PAGE 1): FETAL SOFT TISSUE ALTERATIONS - CAESAREAN-DELIVERED LIVE FETUSES (DAY 21 OF GESTATION) - SUMMARY

DOSAGE GROUP		I	II	III	IV
PICOPREP DRUG PRODUCT (MG/KG/DOSE)a		0 (CONTROL ARTICLE)	230	750	2000
SODIUM PICOSULPHATE (MG/KG/DOSE)a,b		0 (CONTROL ARTICLE)	0.14	0.45	1.2
LITTERS EVALUATED	N	24	22	24	25
FETUSES EVALUATED	N	159	149	160	162
LIVE	N	159	149	160	162
PALATE: CLEFT					
LITTER INCIDENCE	N(%)	0(0.0)	1(4.5)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.7)	0(0.0)	0(0.0)
EYES: RETINA FOLDED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(4.2)	2(8.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.6)	2(1.2)
BRAIN: VENTRICLES, SLIGHT DILATION					
LITTER INCIDENCE	N(%)	1(4.2)	0(0.0)	1(4.2)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.6)	0(0.0)	1(0.6)	0(0.0)
VESSELS: INNOMINATE ARTERY ABSENT					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(4.2)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.6)	0(0.0)

a. Dosage occurred twice daily (BID) approximately 8 hours ± 30 minutes apart on days 7 through 17 of gestation.
b. Based on 10 mg of sodium picosulphate within 16.13 g of drug product.

The following Table 12 (from pages 51-53 of the report) show fetal skeletal alterations.

PROTOCOL XHM00045: ORAL (GAVAGE) EMBRYO-FETAL DEVELOPMENTAL TOXICITY STUDY OF PICOPREP IN RATS

TABLE 12 (PAGE 1): FETAL SKELETAL ALTERATIONS - CAESAREAN-DELIVERED LIVE FETUSES (DAY 21 OF GESTATION) - SUMMARY
(See footnotes on the last page of this table.)

DOSAGE GROUP		I	II	III	IV
PICOPREP DRUG PRODUCT (MG/KG/DOSE)a		0 (CONTROL ARTICLE)	230	750	2000
SODIUM PICOSULPHATE (MG/KG/DOSE)a,b		0 (CONTROL ARTICLE)	0.14	0.45	1.2
LITTERS EVALUATED	N	24	22	24	25
FETUSES EVALUATED	N	172	161	172	175
LIVE	N	172	161	172	175
SKULL: SQUAMOSAL, INCOMPLETELY OSSIFIED					
LITTER INCIDENCE	N(%)	0(0.0)	1(4.5)	1(4.2)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.6)e	1(0.6)g	0(0.0)
SKULL: ZYGOMATIC, INCOMPLETELY OSSIFIED					
LITTER INCIDENCE	N(%)	0(0.0)	1(4.5)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.6)e	0(0.0)	0(0.0)
SKULL: EYE SOCKET, SMALL					
LITTER INCIDENCE	N(%)	0(0.0)	1(4.5)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.6)d	0(0.0)	0(0.0)
SKULL: MANDIBLES, FUSED					
LITTER INCIDENCE	N(%)	0(0.0)	1(4.5)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.6)d	0(0.0)	0(0.0)
SKULL: SUPRAOCCIPITALS, INCOMPLETELY OSSIFIED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(4.2)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.6)g	0(0.0)
CERVICAL VERTEBRAE: ARCH, INCOMPLETELY OSSIFIED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	2(8.3)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	2(1.2)g,h	0(0.0)
CERVICAL VERTEBRAE: CERVICAL RIB PRESENT AT 7TH CERVICAL ARCH					
LITTER INCIDENCE	N(%)	0(0.0)	1(4.5)	2(8.3)	5(20.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.6)	3(1.7)*f	6(3.4)**
CERVICAL VERTEBRAE: ARCH, 6TH CERVICAL ARCH HAS THE APPERANCE OF THE 7TH					
LITTER INCIDENCE	N(%)	1(4.2)	0(0.0)	0(0.0)	1(4.0)
FETAL INCIDENCE	N(%)	1(0.6)c	0(0.0)	0(0.0)	2(1.1)
THORACIC VERTEBRAE: CENTRUM, BIFID					
LITTER INCIDENCE	N(%)	1(4.2)	1(4.5)	1(4.2)	2(8.0)
FETAL INCIDENCE	N(%)	2(1.2)	1(0.6)	1(0.6)	2(1.1)

* Significantly different from the control group value ($p \leq 0.05$).
** Significantly different from the control group value ($p \leq 0.01$).

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PROTOCOL XHM00045: ORAL (GAVAGE) EMBRYO-FETAL DEVELOPMENTAL TOXICITY STUDY OF PICOPREP IN RATS

TABLE 12 (PAGE 2): FETAL SKELETAL ALTERATIONS - CAESAREAN-DELIVERED LIVE FETUSES (DAY 21 OF GESTATION) - SUMMARY
(See footnotes on the last page of this table.)

DOSAGE GROUP		I	II	III	IV
PICOPREP DRUG PRODUCT (MG/KG/DOSE)a		0 (CONTROL ARTICLE)	230	750	2000
SODIUM PICOSULPHATE (MG/KG/DOSE)a,b		0 (CONTROL ARTICLE)	0.14	0.45	1.2
LITTERS EVALUATED	N	24	22	24	25
FETUSES EVALUATED	N	172	161	172	175
LIVE	N	172	161	172	175
LUMBAR VERTEBRAE: ARCH, INCOMPLETELY OSSIFIED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(4.2)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.6)g	0(0.0)
RIBS: INCOMPLETELY OSSIFIED (HYPOPLASTIC)					
LITTER INCIDENCE	N(%)	0(0.0)	1(4.5)	1(4.2)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.6)e	1(0.6)g	0(0.0)
RIBS: THICKENED					
LITTER INCIDENCE	N(%)	1(4.2)	0(0.0)	0(0.0)	1(4.0)
FETAL INCIDENCE	N(%)	1(0.6)c	0(0.0)	0(0.0)	1(0.6)i
RIBS: WAVY					
LITTER INCIDENCE	N(%)	1(4.2)	0(0.0)	0(0.0)	3(12.0)
FETAL INCIDENCE	N(%)	1(0.6)c	0(0.0)	0(0.0)	3(1.7)i
RIBS: SHORT					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	3(12.5)**	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	3(1.7)**f,g	0(0.0)
STERNAL CENTRA: SUMMARIZATION (SUMMARIZATION OF INCOMPLETELY OSSIFIED, ASYMMETRIC AND NOT OSSIFIED)					
LITTER INCIDENCE	N(%)	0(0.0)	1(4.5)	4(16.7)	1(4.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.6)	3(1.7)	1(0.6)
STERNAL CENTRA: INCOMPLETELY OSSIFIED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(4.2)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	2(1.2)h	0(0.0)
STERNAL CENTRA: ASYMMETRIC					
LITTER INCIDENCE	N(%)	0(0.0)	1(4.5)	1(4.2)	1(4.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.6)	1(0.6)	1(0.6)
STERNAL CENTRA: NOT OSSIFIED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(4.2)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.6)	0(0.0)

** Significantly different from the control group value ($p \leq 0.01$).

PROTOCOL XHM00045: ORAL (GAVAGE) EMBRYO-FETAL DEVELOPMENTAL TOXICITY STUDY OF PICOPREP IN RATS

TABLE 12 (PAGE 3): FETAL SKELETAL ALTERATIONS - CAESAREAN-DELIVERED LIVE FETUSES (DAY 21 OF GESTATION) - SUMMARY

FOOTNOTES

a. Dosage occurred twice daily (BID) approximately 8 hours ± 30 minutes apart on days 7 through 17 of gestation.
b. Based on 10 mg of sodium picosulphate within 16.13 g of drug product.
c. Fetus 7118-11 had other skeletal alterations.
d. Fetus 7143-5 had other skeletal alterations.
e. Fetus 7150-3 had other skeletal alterations.
f. Fetus 7152-1 had other skeletal alterations.
g. Fetus 7167-1 had other skeletal alterations.
h. Fetus 7175-11 had other skeletal alterations.
i. Fetus 7189-1 had other skeletal alterations.

Summary: In a Segment II oral embryofetal development study in rats, pregnant female SD rats were treated with PicoPrep at 230, 750 and 2000 mg/kg BID doses. Test article-related reductions in body weights and food consumption were observed at mid and high dose. Clinical signs included soft feces and dehydration and ungroomed coat at mid and high dose. There were no significant treatment-related effects on any intrauterine parameters or C-section parameters. There were no significant treatment-related fetal gross external, visceral or skeletal malformations. There was a dose and treatment-related fetal and litter incidences in the cervical rib at the 7th cervical vertebra.

These alterations were considered a common variation in this strain of rat. PicoPrep was not teratogenic in this study.

Study title: Oral (Gavage) Embryo-Fetal Developmental Study of PicoPrep in Rabbits

Study no.:	XHM00047
Study report location:	EDR 4.2.3.5.2.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 4, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	PicoPrep, Lot 010901T-2, 100%

Key Study Findings:

- In a Segment II oral embryofetal development study in New Zealand white rabbits, pregnant female rabbits were treated with PicoPrep at 230, 460 and 900 mg/kg BID doses.
- Treatment-related mortality occurred at 230 (2 of 20), 460 (3 of 20) and 900 (11 of 20) mg/kg BID PicoPrep doses. Early euthanasia occurred due to poor clinical conditions in 1 and 3 rabbits at 460 and 900 mg/kg BID doses, respectively.
- Treatment-related clinical signs included soft or liquid feces, mucoid feces, and light brown or green colored feces at mid and high doses. In addition, red substance in the cage pan and perivaginal swelling were observed in a significantly increased number at the 900 mg/kg BID dose, in comparison with the control.
- Test article-related reductions in body weight gain and food consumption were observed at mid and high doses.
- Abortions were observed at all doses. The incidences of abortion were 0, 1, 2 and 8 in the 0, 230, 460 and 900 mg/kg BID groups, respectively. Treatment-related abortions were probably attributed to the poor clinical condition, low food consumption, reduced body weight, dehydration, and diarrhea.
- Mean litter size and the mean number of live fetuses per litter was significantly reduced at the high dose while the mean number of resorptions (early, late and total) and pre- and post-implantation loss (mean %) were significantly increased at the high dose, when compared to the respective control.
- There were gross fetal external (one acephalic fetus at the high dose), visceral (intermediate lung lobe absent at mid and high dose including control and gall bladder absent at low and mid dose) and skeletal changes (incomplete ossifications or absence of ossifications of several bones; lumbar vertebrae: centrum fused, small arch; forelimb: metacarpal absent, digit absent, phalanx absent, etc. at the high dose).
- PicoPrep was not teratogenic in this study up to 460 mg/kg BID.

Reference ID: 3130340

Methods: In this study, pregnant female rabbits were randomly assigned to four dosage groups (20/group). PicoPrep or the control article (water) was administered via oral gavage (10 mL/kg) twice daily (8 hours apart) on days 7 through 19 of gestation (DGs 7 through 19) at dosage levels of 0 (Control), 230, 460 and 900 mg/kg BID. Rabbits were euthanized on DG 29, Caesarean-sectioned and examined for gross lesions. The number and distribution of corpora lutea, implantation sites, and live and dead fetuses were recorded. The following parameters were evaluated: viability, clinical observations, body weights and body weight gains, food consumption, necropsy observations, Caesarean-sectioning and litter observations, including fetal sex and body weights, fetal gross external, soft tissue and skeletal alterations and ossification site averages.

Doses:	0, 230, 460 and 900 mg/kg BID*
Frequency of dosing:	Daily
Dose volume:	10 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Deionized Water
Species/Strain:	New Zealand White rabbits
Number/Sex/Group:	20/group
Satellite groups:	None
Study design:	The study design is shown below (from page 24 of the report)
Deviation from study protocol:	There were no protocol deviations that affected the outcome or interpretation of this study.

*: Rationale for Dose selection:

Dosage levels were selected on the basis of a dosage-range embryo-fetal developmental toxicity study of PicoPrep in rabbits (Protocol XHM00046).
In the dose ranging study, twenty-five timed-mated rabbits were randomly assigned to five dosage groups (Groups I through V, n = 5/group). PicoPrep or control article were administered orally via gavage twice daily approximately 8 hours apart from DGs 7 through 19 at 0 (Control Article), 250, 450, 750, and 900 mg/kg BID (10 mL/kg). Treatment-related clinical signs included soft or liquid feces, scant feces, mucoid feces, no feces in cage pan and ungroomed coat. There were reductions in body weight gains and/or body weight losses and reduction in food consumption at 750 and 900 mg/kg BID doses. Postimplantation loss was increased in the 900 mg/kg BID group when compared to control. Mean percentage of postimplantation loss, mean resorptions (early and total) and mean percentage of dead or resorbed conceptuses per litter were increased and mean litter size and mean number of live fetuses were reduced in the 900 mg/kg BID group, in comparison with the respective control group values. One Doe at 900 mg/kg BID group had a litter consisting of only resorbed conceptuses. Mean fetal body weights (male, female and combined) were also reduced in the 900 mg/kg BID group, in comparison with the respective control group values. There were no fetal gross external alterations in any of the fetuses.

Reference ID: 3130340

Based on the results of the dosage-range study, dosages of 230, 460 and 900 mg/kg BID of PicoPrep were selected for the definitive embryo-fetal developmental study (Protocol XHM00047). The lowest dosage level of PicoPrep, 230 mg/kg BID, is the clinical dose of PicoPrep (230 mg/kg, a single administration of PicoPrep in a 70 kg human patient is 16.13 g, which includes 10 mg sodium picosulfate, resulting in a dose of 0.14 mg/kg sodium picosulfate). The highest dosage level, 900 mg/kg BID, represented a >3-fold exposure (AUC) margin and was selected to demonstrate some evidence of maternal toxicity. The middle dosage level, 460 mg/kg BID, represented a 2-fold exposure (AUC) margin and was selected to demonstrate any dose-related responses.

The study design is shown below from page 24 of the study report).

Dosage Group	Number of Rabbits	PICOPREP (Drug Product) Dosage (mg/kg/dose)[a]	Sodium Picosulphate Dosage (mg/kg/dose)[b]	PICOPREP (Drug Product) Concentration (mg/mL)	Dosage Volume (mL/kg/dose)	Assigned Rabbit Numbers
I	20	0 (Control Article)	0 (Control Article)	0	10	8801 - 8820
II	20	230	0.14	23	10	8821 - 8840
III	20	460	0.28	46	10	8841 - 8860
IV	20	900	0.54	90	10	8861 - 8880

a. Doses were administered BID 8 hours apart (±30 minutes).
b. Based on 10 mg of sodium picosulphate within 16.13 g of PICOPREP.

Observations and Results:

Mortality: Mortality was observed for viability twice daily. Treatment-related mortality occurred at 230 (2 of 20), 460 (3 of 20) and 900 (11 of 20) mg/kg BID PicoPrep. Due to adverse clinical condition resulting from reduced food consumption and body weight loss, early euthanasia occurred in 1 and 3 rabbits at 460 and 900 mg/kg BID dose, respectively. Treatment and dose-related abortions were observed at all doses i.e., abortions occurred in 1, 2 and 8 rabbits in 230, 460 and 900 mg/kg BID groups, respectively. There were no abortions in control animals. The high rate of abortions at the high dose were attributed to severe maternal toxicity i.e., reductions in food consumption, body weight loss, dehydration, etc. The applicant stated that the increased toxicity of rabbits compared to rats was due to the sensitivity of rabbits to alterations in the balance in intestinal microflora, which was associated with repeated treatment with PicoPrep. As per the applicant, such sensitivity is species specific and was reported to occur following repeated administration of antibiotics (e.g., norfloxacin).

Clinical Signs: Clinical signs were observed twice daily. Treatment-related clinical signs included soft or liquid feces, mucoid feces, and light brown or green colored feces.

Reference ID: 3130340

Red substance in cage pan and perivaginal swelling were observed in a significantly increased number at 900 mg/kg BID dose, in comparison with the control. Many of the rabbits showing these clinical signs aborted after prolonged periods of body weight loss and severely reduced food consumption resulting from the treatment. The following clinical signs were observed in rabbits at 460 and 900 mg/kg BID groups that were either euthanized due to adverse clinical condition or aborted following prolonged periods of body weight loss and severely reduced food consumption resulting from treatment with PicoPrep: decreased motor activity, lost righting reflex, clear or yellow perinasal substance, ptosis, head kept low to the ground, ataxia, bradypnea, moribund condition and pinnae cold to touch. Yellow perinasal substance was seen in one rabbit at 230 mg/kg BID on a single occasion during the post-treatment period, and was considered treatment related. Orange urine and hunched posture were observed in rabbits at 900 mg/kg BID prior to scheduled termination, and were considered indicative of poor clinical condition resulting from treatment with the test article.

Body Weight: Body weights were recorded on DG 0 and daily during the dosage and postdosage periods. The mean initial (Day 0) and final (Day 28) body weights of control animals were 3.55 and 3.90 kg respectively. At Day 28, maternal body weights were 95%, 99.5% and 91% of control at low, mid and high doses, respectively. During GD 20-29, mean body weight gain was 100%, 164% and 100% of control weight gain (0.14 kg) low, mid and high doses, respectively.

Food Consumption: Food consumption values were recorded on a daily basis. The mean initial (Days 7-10) and final (Days 24-29) food consumptions in control animals were 156.8 and 89.7 g/animal/day, respectively. Mean food consumptions during Days 7-29 were 97%, 94% and 69% of control (121.8 g/animal/day) at low, mid and high doses, respectively.

Toxicokinetics: Not conducted

Dosing Formulation Analysis: In each of the three assays (i.e., sodium picosulfate, citrate/citric acid and magnesium), samples from the first and last days of formulation preparation met acceptance criteria for concentration (i.e., the difference between the actual mean value and the targeted concentration was ≤ 15%) and homogeneity (the relative standard deviation [RSD] for the formulation, calculated as the RSD for the grand mean of the average values for top, middle and bottom locations, was ≤ 5%).

Necropsy: At 900 mg/kg BID, there were increased numbers of rabbits with large gallbladders and/or gallbladders that contained green or white areas, in comparison with the control group. These gross lesions were attributed to the treatment with PicoPrep. The cecum was edematous in one rabbit and contained numerous red areas in two rabbits at 900 mg/kg BID. These gross lesions were also attributed to the treatment.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.): No Caesarean-sectioning or litter parameters were affected by treatment with PicoPrep at 460 mg/kg BID dose. In the surviving rabbits, at 900 mg/kg BID, the mean

Reference ID: 3130340

percentage of post-implantation loss and the mean percentage of dead or resorbed conceptuses per litter were both increased, and mean fetal body weights (male, female and total) were significantly reduced. The litter averages for corpora lutea, implantations, litter sizes, live fetuses, early and late resorptions and percent live male fetuses (data for live female fetuses were not provided) were comparable among the four dosage groups and did not significantly differ. One dead fetus was seen at 900 mg/kg BID group. All placentae appeared normal.

However, when all pregnant female rabbits were included in the evaluation of Caesarean-sectioning and litter parameters, regardless of termination status, mean litter size and the mean number of live fetuses per litter was significantly reduced at the high dose while the mean number of early resorptions, total resorptions, late resorptions and pre- and post-implantation loss (mean %) were significantly increased at the high dose, in comparison with the respective control. The following table (from page 38 of the report) shows the Cesarean section data.

Text Table 2. Caesarean-sectioning Parameters

Dosage (mg/kg/dose)[a]	0 (Control Article)	230	460	900	Historical Control Data[c]
Sodium picosulphate dosage (mg/kg/dose)[a,b]	0 (Control Article)	0.14	0.28	0.54	
Caesarean-sectioning parameters – Excluding early terminations (mean or mean percentage)					
Implantation Sites	9.4	9.9	9.5	8.8	7.5-9.4
Litter Sizes	8.8	9.6	9.0	8.1	7.2-9.2
Live Fetuses	8.8	9.6	9.0	8.0	7.2-9.2
Resorptions	0.6	0.3	0.4	0.7	0.1-0.5
Early resorptions	0.6	0.3	0.2	0.6	0-0.5
Late Resorptions	0.0	0.0	0.2	0.1	0-0.2
% Postimplantation loss	6.4	3.1	4.1	10.7	1.4-4.7
Caesarean-sectioning parameters – Including early terminations (mean or mean percentage)					
Implantation Sites	9.4	9.8	9.7	8.8	7.5-9.4
Litter Sizes	8.8	9.5	9.1	5.8	7.2-9.2
Live Fetuses	8.8	8.6	7.7	3.9**	7.2-9.2
Resorptions	0.6	0.3	0.6	3.0	0.1-0.5
Early resorptions	0.6	0.3	0.3	1.4	0-0.5
Late Resorptions	0.0	0.0	0.3	1.6*	0-0.2
% Postimplantation loss	6.4	12.7	18.5	56.9*	1.4-4.7

a. Dosage occurred twice daily (BID) approximately 8 hours ± 30 minutes apart on days 7 through 19 of gestation.
b. Based on 10 mg of sodium picosulphate within 16.13 g of drug product.
c. (b) (4) 29 historical control data (mean range) from definitive developmental toxicity studies in rabbits (January 2008 to January 2010).
* - ($p \leq 0.05$) ** - ($p \leq 0.01$)

<u>Offspring (Malformations, Variations, etc.)</u>:

<u>Fetal Gross External Alterations</u>:

At 460 mg/kg BID, there were no significant treatment-related gross fetal external, skeletal or visceral changes (malformations or variations). One acephalic (only the tongue, ears and a portion of the brain stem were present) fetus (8870-1) was observed at fetal gross external evaluation at 900 mg/kg BID group, with a variety of associated skeletal alterations (nasal, frontal, maxilla, premaxilla, zygomatic, squamosal, parietal and interparietal not ossified; supraoccipitals incompletely ossified; metacarpals absent, digit absent and phalanx absent). The pollex was absent on each forepaw in this fetus. This fetus had additional skeletal alterations that included incompletely ossified, fused and asymmetric sternal centra; incompletely ossified hyoid alae; wavy alae in the scapulae; unilateral ossification of the centra of lumbar and sacral vertebrae; and incompletely ossified pubes. There were no other fetuses with similar cephalic malformations, and the fetus was observed in the litter of one rabbit that was administered a maternally toxic dosage. Several laboratories (Cozens, DD, 1965, Abnormalities of the External Form and of the Skeleton in the New Zealand White Rabbit, Food Cosmet Toxicol, 3:695-700. Palmer AK, 1968, Spontaneous Malformations of the New Zealand White rabbit: The Background to Safety Evaluation Tests, Lab Anim, 2:195-206. Stadler, J, M-J Kessedjian, J Perraud, 1983, Use of the New Zealand White Rabbit in Teratology: Incidence of Spontaneous and Drug-Induced Malformations. Food Chem Toxicol, 21:631-636) have noted this rare anomaly to occur spontaneously in this strain of laboratory rabbit (fetal incidence of 1 in 1114, 1 in 8500 and 1 in 219). This was considered to be a spontaneous occurrence and unrelated to PicoPrep.

Fetal Visceral Alterations: Visceral alterations included intermediate lung lobe absent (at mid and high doses including control) and gall bladder absent at low and mid dosed.

Fetal Skeletal Alterations: Skeletal alterations at 900 mg/kg BID dose included incomplete ossifications or reduction in ossifications, or absence of ossification of several bones. The skeletal aberrations were generally associated with reductions in ossification. Similar changes have been induced following restricted food consumption (Cappon, GD, TL Fleeman, RE Chapin, and ME Hurtt, 2005, Effects of Feed Restriction During Organogenesis on Embryo-Fetal Development in Rabbit, Birth Defects Res (Part B), 74:424-30). The following table shows fetal external, skeletal and visceral alterations (fetal incidences).

Parameter	**0 mg/kg BID**	**230 mg/kg BID**	**460 mg/kg BID**	**900 mg/kg BID**
Fetuses/Litters Examined	176/20	144/15	154/17	57/7
Fetal External Alterations				
Head: Acephaly	0 (0%)	0 (0%)	0 (0%)	1 (1.8%)
Forelimbs: Digits absent	0 (0%)	0 (0%)	0 (0%)	1 (1.8%)
Fetal Visceral Alterations				
Lungs: Intermediate lobe	3 (1.7%)	0 (0%)	2 (1.3%)	3 (5.4%)

absent				
Gall Bladder: Absent	0 (0%)	1 (0.7%)	1 (0.6%)	0 (0%)
Fetal Skeletal Alterations				
Skull: Irregular ossification	3 (1.7%)	3 (2.1%)	1 (0.6%)	3 (5.4%)
Thoracic Vertebrae				
-Irregularly shaped	1 (0.6%)	0 (0%)	1 (0.6%)	0 (0%)
-Centrum, Bifid	0 (0%)	0 (0%)	2 (1.3%)	0 (0%)
-Centrum, Unilateral ossification	0 (0%)	0 (0%)	2 (1.3%)	0 (0%)
-Centrum, Fused	0 (0%)	0 (0%)	2 (1.3%)	0 (0%)
-Arch, Small	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)
Lumbar Vertebrae				
-Centrum, Fused	0 (0%)	0 (0%)	0 (0%)	1 (1.8%)
-Arch, Small	0 (0%)	0 (0%)	0 (0%)	1 (1.8%)
-Arch, Irregularly shaped	0 (0%)	0 (0%)	0 (0%)	1 (1.8%)
Caudal Vertebrae				
-Misaligned	0 (0%)	1 (0.7%)	1 (0.6%)	0 (0%)
Forelimb				
-Metacarpal, Absent	0 (0%)	1 (0.7%)	0 (0%)	1 (1.8%)
-Digit, Absent	0 (0%)	1 (0.7%)	0 (0%)	1 (1.8%)
-Phalanx, Absent	0 (0%)	1 (0.7%)	0 (0%)	1 (1.8%)

Summary: In a Segment II oral (gavage) embryofetal development study in rabbits, pregnant female New Zealand white rabbits were treated with PicoPrep at 230, 460 and 900 mg/kg BID doses. Maternal toxicity was seen at all doses (230, 460 and 900 mg/kg BID) characterized primarily by reduction in food consumption, body weight loss, dehydration, abortion and/or death. The incidence and severity of the poor clinical condition was dose-related. Similarly, the incidence of abortion was 0, 1, 2 and 8 in the 0, 230, 460 and 900 mg/kg BID groups, respectively. Treatment-related abortions were attributed to the poor maternal clinical conditions e.g., low food consumption, reduced body weight, dehydration, and diarrhea. The rabbit appeared to be more sensitive to the toxicity of PicoPrep than rats in the Segment II studies. The applicant stated that the toxicity was considered to be due to the sensitivity of rabbits to alterations in the balance in the intestinal microflora. Such species specific sensitivity was reported (Clark RL, RT Robertson, CP Peter, JA Bland, TE Nolan, L Oppenheimer, DL Bokelman, 1986, Association between Adverse Maternal and Embryo-Fetal Effects in Norfloxacin-Treated and Food Deprived Rabbits. Fund Appl Toxicol, 7:1-15) to occur following repeated administration of antibiotics (e.g., Norfloxacin). A maternal NOAEL could not

be established as treatment-related adverse effects were seen at all doses. Fetal external, visceral and skeletal alterations were seen at the high dose of 900 mg/kg BID, which caused significant maternal toxicity. All other fetal alterations were considered unrelated to the treatment because of the following reasons: 1) the alteration occurred only in the control group or at an incidence that was comparable to the control article group; 2) the litter incidence, the more relevant parameter [ICH S5(R2), November, 2005, Guideline for Industry: Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility], did not reflect a dose-related effect; 3) the litter incidence was within the range of historical control data for the testing facility; and/or 4) the fetal alteration was considered a common variation in this strain of rabbit (Christian MS, RJ McCarty, DK Cox-Sica, and CP Cao, 1987, Recent Increases in the Incidence of Skull, Lung and Rib Alterations in Vehicle Control New Zealand White Rabbits [Abstract]. Proceeding of the eighth Annual Meeting of the American College of Toxicology; Baltimore, Maryland; Dec 7-9. J Am Coll Toxicol, 6(3). Khera KS, 1981, Common Fetal Aberrations and their Teratologic Significance: A Review. Fund Appl Toxicol, 1:13-8). Overall, PicoPrep was not teratogenic in rabbits up to 460 mg/kg BID.

9.3 Prenatal and Postnatal Development

Study title: Oral (Gavage) Developmental and Perinatal/Postnatal Reproduction Toxicity Study of PicoPrep in Rats, Including a Postnatal Behavioral/Functional Evaluation

Study no.:	XHM00049
Study report location:	EDR 4.2.3.5.3.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	April 27, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	PicoPrep, 010901T-2, 100%

Key Study Findings:

- In a pre and postnatal development study in rats, animals were administered PicoPrep by oral gavage at 230, 750 and 2000 mg/kg BID doses.
- There were no treatment-related mortalities of the F0 rats. Clinical signs at the mid and high doses in the F0 rats included ungroomed coat, dehydration and soft feces, which were attributed to the pharmacological effect of PicoPrep.
- There were reductions in body weight and food consumptions at the mid and high dose of the F0 rats.
- The number of dead pups was increased with the dose and the viability index was reduced at the high dose compared to that of the control.

Reference ID: 3130340

- There were no significant treatment-related effects on the F1 generation growth and development and neurobehavioral tests (learning and memory as evaluated in passive avoidance and water maze tests).
- There were no significant treatment-related effects on F2 generation fetal gross external evaluations.

Methods: One hundred female rats were randomly assigned to four dosage groups (25/group). PicoPrep or the control article (deionized water) was administered at 230, 750 and 2000 mg/kg via oral gavage (10 mL/kg) twice daily (BID, 8 hours apart) from day 7 of presumed gestation (DG 7) through day 20 of lactation (DL 20) or DG 24 (rats that did not deliver a litter). During cohabitation, female rats were paired with breeder male rats, one male rat per female rat. The cohabitation period consisted of a maximum of five days. After completion of the 21-day postpartum period (DL 21), female rats were euthanized, and a gross necropsy of the thoracic, abdominal and pelvic viscera was performed. The F1 generation rats selected for continued observation were weaned on DL 21. The F1 generation rats not selected for continued observation were euthanized on DL 21, and a gross necropsy of the thoracic, abdominal and pelvic viscera was performed (including a cross-section of the head to evaluate the brain). F1 generation rats were mated and F2 generation rats were evaluated for the following parameters: mortality, body weight, male/female ratio and external alterations.

Doses:	230, 750 and 2000 mg/kg* BID
Frequency of dosing:	BID, 8 hours apart
Dose volume:	10 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Deionized Water
Species/Strain:	SD rats
Number/Sex/Group:	25/group
Satellite groups:	None
Study design:	Study design is shown below (from page 30 of the report)
Deviation from study protocol:	There were no deviations that affected the outcome or interpretation of this study.

Reference ID: 3130340

4.5.1.1. F0 Generation Rats

Dosage Group	Number of Rats	PICOPREP (Drug Product) Dosage (mg/kg/dose)[a]	Sodium Picosulphate Dosage (mg/kg/dose)[b]	PICOPREP (Drug Product) Concentration (mg/mL)	Dosage Volume (mL/kg/dose)	Assigned Rat Numbers
I	25	0 (Control Article)	0 (Control Article)	0	10	1401 - 1425
II	25	230	0.14	23	10	1426 - 1444, 16768[c], 1446 - 1450
III	25	750	0.45	75	10	1451 - 1475
IV	25	2000	1.2	200	10	1476 - 1500

a. Doses were administered BID 8 hours apart (±30 minutes).
b. Based on 10 mg of sodium picosulphate within 16.13 g of PICOPREP.
c. Due to body weight loss, rat 1455 was excluded from study on DG 7 and replaced with rat 16768.

4.5.1.2. F1 Generation Rats

Maternal Dosage Group	Maternal PICOPREP (Drug Product) Dosage (mg/kg/dose)[a]	Number of Rats Per Sex	Assigned F1 Generation Rat Numbers	
			Male Rats	Female Rats
I	0 (Control Article)	25	5701 - 5725	5801 - 5825
II	230	25	5726 - 5750	5826 - 5850
III	750	25	5751 - 5775	5851 - 5875
IV	2000	25	5776 - 5800	5876 - 5900

a. F0 generation maternal doses were administered BID 8 hours apart (±30 minutes).

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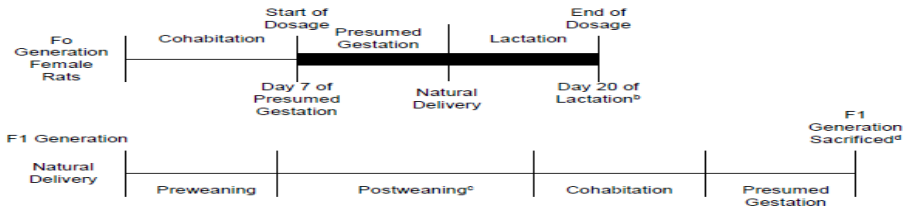
DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY[a]



Dosage Period

a. For additional details see "Tests, Analyses and Measurements" section of the protocol.
b. F0 generation rats sacrificed day 21 of lactation.
c. Behavioral and functional assessments.
d. Fetal evaluations (all fetuses - external examinations).

*****Rationale for Dosage Selection: Dosages were selected on the basis of a dosage-range developmental toxicity study (Protocol XHM00044), which was discussed before.

Observations and Results:

Reference ID: 3130340

F_0 Dams:

Survival: Rats were observed daily for mortality. One rat at 2000 mg/kg BID was found dead on Day 24 and one rat at 750 mg/kg BID was sacrificed on Day 24 of presumed gestation. The cause of death was not mentioned. However, the applicant stated that there was no treatment-related death.

Clinical signs: Clinical signs were recorded on a daily basis. Treatment-related clinical signs included soft or liquid feces and mucoid feces at mid and high doses. Other clinical signs included ungroomed coat, dehydration, red perineal area, scant feces and urine-stained abnormal fur at mid- and high doses. Theses clinical signs were seen in a transient manner at the low dose.

Body weight: Body weight was recorded on a weekly basis. The mean initial (Day 0) and final (Day 20) body weights were 233.8 and 391.4 g, respectively. At Day 20, mean body weights were 99.5%, 93% and 94% of control at low, mid and high doses, respectively. At Day 20, mean body weight gains were 99%, 85% and 85% of control (157.7 g) at low, mid and high doses, respectively.

Food consumption: Food consumption values were recorded on DGs 0, 7, 10, 12, 15, 18, 20 and 25 (if necessary) and DLs 1, 4, 7, 10 and 14. The mean initial (Day 0-7) and final (Day 18-20) food consumptions were 22.6 and 23.2 g/animal/day, respectively. Mean food consumption values during Days 0-20 were 100%, 87% and 88% of control (23.7 g/animal/day) at low, mid and high doses, respectively.

Uterine content: After completion of the 21-day postpartum period, female rats were euthanized and a gross necropsy of the thoracic, abdominal and pelvic viscera was performed. Pregnancy occurred in 24 to 25 rats in each dosage group. There were 24, 25, 24 and 23 dams that delivered litters in the 0, 230, 750 and 2000 mg/kg BID groups, respectively. No dams had all pups died before scheduled euthanasia on DL 21. The number of pups found dead increased with increase in dose, and consequently, the viability index was reduced at 2000 mg/kg BID, in comparison with the control article group values. Mean pup weights per litter were reduced by as much as 15% at 2000 mg/kg BID during the preweaning period, in comparison with the

respective control group values. Values for the numbers of dams delivering litters, the durations of gestation, averages for implantation sites per delivered litter, dams with stillborn pups, gestation indices, dams with all pups dying, pups delivered, liveborn and stillborn pups, lactation indices, surviving pups per litter, percent male pups per number of pups sexed and live litter sizes at weighing were generally comparable among the four dosage groups and did not significantly differ. Data are show in Tables A11 and A12 (from page 75-76 of the report) below.

Necropsy observation: There were no significant treatment-related findings

Toxicokinetics: Not conducted

Dosing Formulation Analysis: In each of the three assays (i.e., sodium picosulfate, citrate/citric acid and magnesium), samples from the first and last days of formulation preparation met acceptance criteria for concentration (i.e., the difference between the actual mean value and the targeted concentration was ≤ 15%) and homogeneity (i.e., the relative standard deviation [RSD] for the formulation, calculated as the RSD for the grand mean of the average values for top, middle and bottom locations, was ≤ 5%).

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TABLE A11 (PAGE 1): NATURAL DELIVERY OBSERVATIONS - SUMMARY - F0 GENERATION FEMALE RATS

DOSAGE GROUP		I	II	III	IV
PICOPREP DRUG PRODUCT (MG/KG/DOSE)a		0 (CONTROL ARTICLE)	230	750	2000
SODIUM PICOSULPHATE (MG/KG/DOSE)a,b		0 (CONTROL ARTICLE)	0.14	0.45	1.2
RATS ASSIGNED TO NATURAL DELIVERY	N	25	25	25	25
PREGNANT	N(%)	24(96.0)	25(100.0)	24(96.0)	24(96.0)
INCLUDED IN ANALYSES	N	24	25	24	23c
DELIVERED A LITTER	N(%)	24(100.0)	25(100.0)	24(100.0)	23(100.0)
DURATION OF GESTATION d	MEAN±S.D.	22.6 ± 0.5	22.5 ± 0.5	22.5 ± 0.5	22.7 ± 0.5
IMPLANTATION SITES	N	380	395	364	360
PER DELIVERED LITTER	MEAN±S.D.	15.8 ± 1.6	15.8 ± 1.7	15.2 ± 1.5	15.6 ± 1.5
DAMS WITH STILLBORN PUPS	N(%)	2(8.3)	2(8.0)	3(12.5)	1(4.3)
DAMS WITH NO LIVEBORN PUPS	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
GESTATION INDEX e	%	100.0	100.0	100.0	95.8
	N/N	24/ 24	25/ 25	24/ 24	23/ 24
DAMS WITH ALL PUPS DYING DAYS 1-4 POSTPARTUM	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
DAMS WITH ALL PUPS DYING DAYS 5-21 POSTPARTUM	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

a. Dosage occurred twice daily (BID) approximately 8 hours ± 30 minutes apart on day 7 of gestation through day 20 of lactation.
b. Based on 10 mg of sodium picosulphate within 16.13 g of drug product.
c. Excludes values for dam 1486, which was found dead on day 24 of gestation.
d. Calculated (in days) as the time elapsed between confirmed mating (arbitrarily defined as day 0 of gestation) and the day the first pup was delivered.
e. Number of rats with live offspring/number of pregnant rats.

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TABLE A12 (PAGE 1): LITTER OBSERVATIONS (NATURALLY DELIVERED PUPS) - SUMMARY - F1 GENERATION LITTERS

DOSAGE GROUP		I	II	III	IV
PICOPREP DRUG PRODUCT (MG/KG/DOSE)a		0 (CONTROL ARTICLE)	230	750	2000
SODIUM PICOSULPHATE (MG/KG/DOSE)a,b		0 (CONTROL ARTICLE)	0.14	0.45	1.2
DELIVERED LITTERS WITH ONE OR MORE LIVEBORN PUPS	N	24	25	24	23
PUPS DELIVERED (TOTAL)	N	351	371	338	344
	MEAN±S.D.	14.6 ± 1.9	14.8 ± 2.2	14.1 ± 1.7	15.0 ± 1.5
LIVEBORN	MEAN±S.D.	14.5 ± 2.0	14.8 ± 2.2	13.9 ± 1.9	14.9 ± 1.6
	N(%)	349(99.4)	369(99.5)	334(98.8)	342(99.4)
STILLBORN	MEAN±S.D.	0.1 ± 0.3	0.1 ± 0.3	0.2 ± 0.5	0.1 ± 0.4
	N(%)	2(0.6)	2(0.5)	4(1.2)	2(0.6)
PUPS FOUND DEAD					
DAY 1	N/N(%)	0/349(0.0)	4/369(1.1)	2/334(0.6)	4/342(1.2)
DAYS 2- 4	N/N(%)	4/349(1.1)	1/365(0.3)	5/332(1.5)	11/338(3.2)**
DAYS 5- 7	N/N(%)	1/345(0.3)	0/364(0.0)	0/327(0.0)	1/327(0.3)
DAYS 8-14	N/N(%)	0/344(0.0)	0/364(0.0)	0/327(0.0)	1/326(0.3)
DAYS 15-18	N/N(%)	0/344(0.0)	1/364(0.3)	0/327(0.0)	0/325(0.0)
DAYS 19-21	N/N(%)	0/344(0.0)	0/363(0.0)	0/327(0.0)	0/325(0.0)
VIABILITY INDEX c	%	98.8	98.6	97.9	95.6**
	N/N	345/349	364/369	327/334	327/342
LACTATION INDEX d	%	99.7	99.7	100.0	99.4
	N/N	344/345	363/364	327/327	325/327

DAY(S) = DAY(S) POSTPARTUM
a. Dosage occurred twice daily (BID) approximately 8 hours ± 30 minutes apart on day 7 of gestation through day 20 of lactation.
b. Based on 10 mg of sodium picosulphate within 16.13 g of drug product.
c. Number of live pups on day 4 postpartum/number of liveborn pups on day 1 postpartum.
d. Number of live pups on day 21 postpartum/number of live pups on day 4 postpartum.
** Significantly different from the control group value ($p \leq 0.01$).

F_1 Generation:

Survival: Mortality was checked twice daily. There were no mortalities. One F1 generation male rat (#5794) at 2000 mg/kg BID was euthanized due to adverse clinical condition on PND 94. This male rat was observed with a broken snout and was humanely euthanized. One F1 generation female rat (#5900) at 2000 mg/kg BID was euthanized due to adverse clinical condition on PND 31 due to a fractured tibia. One F1 generation female rat (#5867) at 750 mg/kg BID was euthanized due to adverse clinical condition on PND 94. This female rat was humanely euthanized due to a broken palate.

Clinical signs: Clinical signs were observed once daily. There were no significant treatment-related clinical signs.

Body weight: Body weights were recorded on a weekly basis. The mean initial (Day 22) and final (Day 120) body weight of control males were 44.9 g and 581.6 g, respectively. The mean initial (Day 22) and final (Day 92) body weights were 44.5 and 273.4 g, respectively. There were no significant treatment-related effects.

Food consumption: Food consumption was recorded on a weekly basis. The mean initial (Day 22-29) and final (Day 85-92) absolute food consumption of control males were 13.7 and 26.3 g/animal/day, respectively. The mean initial (Day 22-29) and final (Day 85-92) absolute food consumption of control females were 13.1 and 21.3 g/animal/day, respectively. There were no significant treatment-related effects.

Physical development: Female rats were evaluated for the age of vaginal patency, beginning on PND 28. Male rats were evaluated for the age of preputial separation, beginning on PND 39. There were no significant treatment-related effects including sexual maturation (preputial separation and vaginal patency).

Neurological assessment: Beginning at PND 24, one male rat and one female rat from each litter were evaluated in a passive avoidance test for learning, short-term retention and long-term retention. Beginning at approximately PND 70, one male rat and one female rat from each litter were evaluated in a water-filled M-maze for overt coordination, swimming ability, learning and memory. There were no significant treatment-related effects on passive avoidance and water maze performance.

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Reproduction: At approximately 90 days of age, the F1 generation rats within each dosage group were assigned to cohabitation period consisted of a maximum of 21 days. Female rats with spermatozoa observed in a smear of the vaginal contents and/or a copulatory plug observed *in situ* were considered to be at DG 0. There were no significant treatment-related effects on mating and fertility. The litter averages for corpora lutea, implantations, percentage of preimplantation loss, litter sizes, live fetuses, early and late resorptions, percentage of postimplantation loss, percentage of live male fetuses per litter, fetal body weights and the percentage of resorbed conceptuses were comparable among the four maternal dosage groups and did not significantly differ. No dam had a litter consisting of only resorbed conceptuses. The following Table B23 (from page 199 of the report) shows the F1 Caesarean –sectioning data.

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TABLE B23 (PAGE 1): CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY - F1 GENERATION FEMALE RATS

MATERNAL DOSAGE GROUP		I	II	III	IV
PICOPREP DRUG PRODUCT (MG/KG/DOSE)		0 (CONTROL ARTICLE)	230	750	2000
SODIUM PICOSULPHATE (MG/KG/DOSE)		0 (CONTROL ARTICLE)	0.14	0.45	1.2
RATS TESTED	N	25	25	24a	24a
PREGNANT	N(%)	25(100.0)	22(88.0)	24(100.0)	22(91.2)
RATS PREGNANT AND CAESAREAN-SECTIONED ON DAY 21 OF GESTATION	N	25	22	24	22
CORPORA LUTEA	MEAN±S.D.	17.0 ± 2.3	16.3 ± 2.2	16.2 ± 3.1	16.5 ± 3.6
IMPLANTATIONS	MEAN±S.D.	16.4 ± 1.9	15.6 ± 2.1	15.2 ± 3.1	15.2 ± 3.7
% PREIMPLANTATION LOSS	MEAN±S.D.	3.0 ± 6.9	3.7 ± 5.2	6.5 ± 9.4	9.0 ± 18.5
LITTER SIZES	MEAN±S.D.	16.0 ± 2.0	15.1 ± 2.3	14.4 ± 3.1	14.6 ± 3.5
LIVE FETUSES	N	400	331	347	322
	MEAN±S.D.	16.0 ± 2.0	15.0 ± 2.3	14.4 ± 3.1	14.6 ± 3.5
DEAD FETUSES	N	0	1	0	0
	MEAN±S.D.	0.0 ± 0.0	0.0 ± 0.2	0.0 ± 0.0	0.0 ± 0.0
RESORPTIONS	MEAN±S.D.	0.4 ± 0.7	0.5 ± 0.7	0.8 ± 0.7	0.6 ± 0.9
EARLY RESORPTIONS	N	10	12	18	13
	MEAN±S.D.	0.4 ± 0.7	0.5 ± 0.7	0.8 ± 0.7	0.6 ± 0.9
LATE RESORPTIONS	N	0	0	0	0
% POSTIMPLANTATION LOSS	MEAN±S.D.	2.4 ± 4.1	3.8 ± 5.0	5.4 ± 5.7	3.5 ± 5.3
DAMS WITH ANY RESORPTIONS	N(%)	8(32.0)	10(45.4)	14(58.3)	8(36.4)
DAMS WITH ALL CONCEPTUSES DEAD OR RESORBED	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
DAMS WITH VIABLE FETUSES	N(%)	25(100.0)	22(100.0)	24(100.0)	22(100.0)
PLACENTAE APPEARED NORMAL	N(%)	25(100.0)	22(100.0)	24(100.0)	22(100.0)

% PREIMPLANTATION LOSS = [(NUMBER OF CORPORA LUTEA - NUMBER OF IMPLANTATIONS) / NUMBER OF CORPORA LUTEA] x 100
% POSTIMPLANTATION LOSS = [(NUMBER OF IMPLANTATIONS - NUMBER OF LIVE FETUSES) / NUMBER OF IMPLANTATIONS] x 100
a. Excludes values for rats that were sacrificed due to adverse clinical observations.

F_2 Generation:

Survival: There were no significant treatment-related effects on survival. Mean number of live fetuses were 16, 15, 14.4 and 14.6 at control, low, mid and high doses, respectively.

Body weight: There were no significant treatment-related effects on body weight.

External evaluation: There were no significant effects on gross external alterations. One fetus had tail pedunculated at the high dose.

Male/Female ratio: There were no significant treatment-related effects on male/female ratio.

F2 data (litter observation and external observation) are shown below (from page 200 and 201 of the report).

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TABLE B24 (PAGE 1): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - SUMMARY - F2 GENERATION LITTERS

MATERNAL DOSAGE GROUP		I	II	III	IV
PICOPREP DRUG PRODUCT (MG/KG/DOSE)		0 (CONTROL ARTICLE)	230	750	2000
SODIUM PICOSULPHATE (MG/KG/DOSE)		0 (CONTROL ARTICLE)	0.14	0.45	1.2
LITTERS WITH ONE OR MORE LIVE FETUSES	N	25	22	24	22
IMPLANTATIONS	MEAN±S.D.	16.4 ± 1.9	15.6 ± 2.1	15.2 ± 3.1	15.2 ± 3.7
LIVE FETUSES	N	400	331	347	322
	MEAN±S.D.	16.0 ± 2.0	15.0 ± 2.3	14.4 ± 3.1	14.6 ± 3.5
% LIVE MALE FETUSES/LITTER	MEAN±S.D.	51.4 ± 10.2	51.3 ± 14.0	51.0 ± 13.9	47.1 ± 19.0
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN±S.D.	5.31 ± 0.24	5.40 ± 0.33	5.36 ± 0.39 [23]a	5.43 ± 0.46
MALE FETUSES	MEAN±S.D.	5.48 ± 0.26	5.53 ± 0.35	5.48 ± 0.38 [23]a	5.47 ± 0.31 [21]b
FEMALE FETUSES	MEAN±S.D.	5.13 ± 0.24	5.25 ± 0.31	5.20 ± 0.41 [23]a	5.30 ± 0.50
% DEAD OR RESORBED CONCEPTUSES/LITTER	MEAN±S.D.	2.4 ± 4.1	3.8 ± 5.0	5.4 ± 5.7	3.5 ± 5.3

[ ] = NUMBER OF VALUES AVERAGED
a. Excludes values for litter 5871; fetal body weights were not collected for fetuses assigned to alcohol (see deviation).
b. Litter 5887 had no male fetuses.

TABLE B25 (PAGE 1): FETAL GROSS EXTERNAL ALTERATIONS - CAESAREAN-DELIVERED LIVE FETUSES (DAY 21 OF GESTATION) - SUMMARY - F2 GENERATION LITTERS/FETUSES

MATERNAL DOSAGE GROUP		I	II	III	IV
PICOPREP DRUG PRODUCT (MG/KG/DOSE)		0 (CONTROL ARTICLE)	230	750	2000
SODIUM PICOSULPHATE (MG/KG/DOSE)		0 (CONTROL ARTICLE)	0.14	0.45	1.2
LITTERS EVALUATED	N	25	22	24	22
LITTERS WITH LIVE FETUS(ES)	N	25	22	24	22
FETUSES EVALUATED	N	400	332	347	322
LIVE	N	400	331	347	322
DEAD	N	0	1a	0	0
BODY: EDEMA					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(4.2)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.3)c	0(0.0)
BODY: TRUNK SHORT					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(4.2)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.3)c	0(0.0)
BODY: NO ANAL OPENING PRESENT					
LITTER INCIDENCE	N(%)	1(4.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.2)b	0(0.0)	0(0.0)	0(0.0)
TAIL: ABSENT					
LITTER INCIDENCE	N(%)	1(4.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.2)b	0(0.0)	0(0.0)	0(0.0)
TAIL: PEDUNCULATED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.5)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.3)

a. Dead fetus was excluded from summarization and statistical analyses. Observations for this conceptus are cited on Table B47.
b. Fetus 5825-3 had other gross external alterations.
c. Fetus 5851-10 had other gross external alterations.

Summary: In a pre and postnatal development (Segment III) study in rats, animals were administered PicoPrep by oral gavage at 230, 750 and 2000 mg/kg BID doses. There were no treatment-related mortalities of the F0 rats. Clinical signs at the mid and high doses in the F0 rats included ungroomed coat, dehydration and soft feces, which were attributed to the pharmacological effect of PicoPrep. There were reductions in body weight and food consumptions at the mid and high dose. The number of dead pups was increased with the dose and the viability index was reduced at the high dose when compared to that of the control. There were no significant treatment-related effects on the F1 generation growth and development and neurobehavioral tests (learning and memory as evaluated in passive avoidance and water maze tests),

Caesarean-sectioning and litter observations. There were no significant treatment-related effects on F2 generation fetal gross external evaluations.

10 Special Toxicology Studies

The following is incorporated from the pharmacology review of IND 101738 dated March 23, 2010.

> Local Tolerance: Sodium picosulfate can cause skin and mucous membrane irritation. However, there is no evidence of an irritant effect on the eye, and no skin sensitizing effect is known ([redacted] (b) (4) sodium picosulfate: Material Safety Data Sheet). Local tolerance at the intended therapeutic site has been investigated in rats that received sodium picosulfate by oral gavage at a dosage of 10 mg/kg/day for up to 12 weeks [Geboes, K., Nijs, G., Mengs, O., Geboes, K.PJ., Van Damme, A. & de Witte, P. 1993. Pharmacology, 47 (Suppl. 1), 187-195; Geboes, K. 1995. Verh.K.Acad.Geneeskd.Belg., 57, 51-75]. Intestinal epithelial cell damage and proliferation were assessed following 2, 6 and 12 weeks of treatment. There were no adverse effects on ileal and colonic epithelial cells, and no effects on cell proliferation as assessed by bromodeoxyuridine (BrdUrd) uptake.

11 Integrated Summary and Safety Evaluation

The applicant has conducted nonclinical studies with sodium picosulfate (major active ingredient of PicoPrep) which included oral 14-day toxicology studies in rats and dogs and genotoxicity studies. In addition, the applicant also conducted toxicology studies with the drug product, PicoPrep, which included 28-day oral toxicology studies in rats and dogs and reproductive toxicology studies, i.e., fertility and early embryonic development to implantation (Segment I) study in rats, embryofetal development (Segment II) studies in rats and rabbits and pre and postnatal development (Segment III) study in rats.

Sodium picosulfate

In rats, sodium picosulfate and it metabolites were not detected in either serum or urine, but high concentrations of sodium picosulfate were found in the feces. As discussed before, sodium picosulfate was metabolized by bacteria present in the colon to form the active compound, BHPM. The mean recovery of sodium picosulfate in the feces was about 74% of the administered dose in 24 hours. About 2% of hydrolysis product, BHPM, was also found in the feces. No sodium picosulfate was recovered in the urine; however, a low concentration (0.067%) of the hydrolysis product was present in the urine.

Reference ID: 3130340

Oral, intraperitoneal (IP) and subcutaneous (SC) LD50 values for sodium picosulfate in rats were reported to be 5000, 3000 and 6980 mg/kg, respectively.

In the 14-day oral (gavage) toxicology study (XHM00037) in rats, animals were treated with sodium picosulfate at 30, 300 and 1000 mg/kg BID doses. The target organs appeared to be the small and large intestines (mucosal hyperplasia at all doses and lymphocytic infiltration at ≥ 300 mg/kg BID).

In another 1-, 5- and 14-day oral (gavage) study (XHM00042) in rats, sodium picosulfate was administered orally at 1.5, 15, 30, and 300 mg/kg BID. Sodium picosulfate produced soft or mucoid stools and diarrhea. Target organs appeared to be the intestine (mucosal hyperplasia, submucosal edema, and lymphoplasmacytic infiltration). The incidences and severity of these histopathology findings were greater in females than males. Following the 14-day recovery periods, all histopathology findings were recovered except for females in the cecum.

In a 14-day oral toxicology study (XHM00039) in dogs, animals were treated with sodium picosulfate at 15, 150 and 600 mg/kg BID doses. Clinical signs included soft stool and diarrhea at mid- and high-dose. The target organ could not be identified in the absence of any significant treatment-related histopathology findings.

Sodium picosulfate was not mutagenic in Ames test, mouse lymphoma assay and did not induce micronuclei in mouse bone marrow micronucleus test. No carcinogenicity studies have been performed with PicoPrep since it is intended for short-term use.

The applicant did not conduct any reproductive toxicology study with sodium picosulfate. However, the applicant provided literature references, which is discussed here. In oral fertility studies in rats and rabbits, sodium picosulfate did not show any significant adverse effect on mating performance and fertility at dosage levels up to 100 mg/kg/day. Sodium picosulfate was not teratogenic in rats up to 10,000 mg/kg/day and in rabbits at doses up to 1000 mg/kg/day, PO. In a peri and postnatal development study in rats, animals were treated with sodium picosulfate at 1, 10, and 100 mg/kg/day. There were an increased number of dead pups at birth at 100 mg/kg/day. Postweaning growth, development, behavior and reproductive functions were unaffected by the treatment with sodium picosulfate.

PicoPrep

In a 28-day oral gavage study (XHM00052) with PicoPrep in rats, animals were administered 230, 750 and 2000 mg/kg BID doses. The target organ could not be identified in the absence of any significant histopathology findings. The NOAEL was considered to be 2000 mg/kg BID.

In a 28-day oral gavage study (XHM00053) with PicoPrep in dogs, animals were administered 230, 500 and 1000 mg/kg BID doses. The target organ could not be

Reference ID: 3130340

identified in the absence of any significant histopathology findings. The NOAEL was considered to be 1000 mg/kg BID.

In an oral fertility and early embryonic development to implantation study (XHM00048) in rats, animals were treated with PicoPrep at 230, 750 and 2000 mg/kg BID. There were no significant treatment-related effects on fertility and reproductive performances in both sexes. In an embryofetal development study (XHM00045) with PicoPrep in rats at 230, 750 and 2000 mg/kg BID, PicoPrep was not teratogenic. In an embryofetal development study (XHM00047) study in rabbits, pregnant female New Zealand white rabbits were treated with PicoPrep at 230, 460 and 900 mg/kg BID doses. Administration of the test article was associated with maternal toxicity at all dosage groups (230, 460 and 900 mg/kg BID) characterized primarily by reduction in food consumption, body weight loss, dehydration, abortion and/or death. The incidence and severity of the poor clinical condition was dose-related. Similarly, the incidence of abortion was 0, 1, 2 and 8 in the 0, 230, 460 and 900 mg/kg BID groups, respectively. Treatment-related abortions were attributed to the poor clinical conditions e.g., low food consumption, reduced body weight, dehydration, diarrhea, etc. A maternal NOAEL could not be established as treatment-related adverse effects were seen at all doses. Fetal external, visceral and skeletal alterations were seen at the high dose, which caused significant maternal toxicity. Overall, PicoPrep was not teratogenic in rabbits up to 460 mg/kg BID dose. In an oral (gavage) pre and postnatal development study (XHM00049) with PicoPrep at 230, 750 and 2000 mg/kg BID doses, the number of dead pups was increased with the dose and the viability index was reduced at the high dose when compared to that of the control. There were no significant treatment-related effects on the F1 generation growth and development and neurobehavioral tests (learning and memory as evaluated in passive avoidance and water maze tests). There were no significant treatment-related effects on F2 generation gross external evaluations. Overall, PicoPrep did not have significant adverse effect on pre and postnatal development in rats.

The NOAEL of 2000 mg/kg BID of PicoPrep in the rat resulted in approximately 3 times and 30 times the systemic exposure of sodium picosulfate and BHPM, respectively, than that in humans (at 230 mg/kg BID). The comparison between the systemic exposure at 1000 mg/kg BID in the dog to the exposure in humans at the clinical dose of PicoPrep (230 mg/kg BID, as given in study FE00017) shows that the NOAEL of this study provides approximately 135-600 times and 12-21 times the systemic exposure of sodium picosulfate and BHPM, respectively, as compared to humans. Summaries of exposure data is shown below (from page 17 of Section 2.4 of the submission).

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Table 3. Comparison of exposure of sodium picosulfate in rat, dog and human.

Species	PICOPREP Dose Level (mg/kg BID[a])	Sodium Picosulfate Dose Level (mg/kg BID[b])	Description	Sodium Picosulfate Cmax (ng/mL)	Sodium Picosulfate AUC (0-t)[c] (ng*h/mL)	Safety margin (Cmax/AUC)
Rat	2000	1.24	NOAEL	14.00-14.01	60.75-118.1	4.4/1.6-3.1
Dog	1000	0.61	NOAEL	284-1119	5109-23080	89-350/135-611
Human	230	0.14	TD	3.2	37.8	-

[a]Doses were administered approximately 8 hours apart in rats and dogs and 6 hours apart in the human study.
[b]Based on 10 mg of sodium picosulfate within 16.13 g of drug product.
[c] Mean values for males and females are combined. 0-t in rat and dog = 24 h. 0-t in human = 0-72 h.

Table 4. Comparison of exposure of BHPM in rat, dog and human.

Species	PICOPREP Dose Level (mg/kg BID[a])	Sodium Picosulfate Dose Level (mg/kg BID[b])	Description	BHPM Cmax (ng/mL)	BHPM AUC (0-t)[c] (ng*h/mL)	Safety margin (Cmax/AUC)
Rat	2000	1.24	NOAEL	1.36-1.52	17.5- 23.85	27-30/26-36
Dog	1000	0.61	NOAEL	1.27-1.37	8.3-13.9	25-27/12-21
Human[d]	230	0.14	TD	0.05	0.67	-

[a]Doses were administered approximately 8 hours apart in rats and dogs and 6 hours apart in the human study.
[b]Based on 10 mg of sodium picosulfate within 16.13 g of drug product.
[c] Mean values for males and females are combined. 0-t in human = 0-72 h. 0-t in rat and dog= 24 h.
[d]Cmax and AUC values are based on mean values for 3 subjects, as 13 subjects were below LLOQ.

Overall, nonclinical safety of PicoPrep has been adequately tested in several toxicology studies with sodium picosulfate and PicoPrep. When PicoPrep, the drug product, was tested in rats and dogs, the NOAELs were 2000 mg/kg BID (about 8 times the recommended clinical dose of 16.1 g BID or 533 mg/kg based on a 60-kg body weight) and 1000 mg/kg BID (about 4 times the recommended clinical dose of 16.1 g BID or 533 mg/kg based on a 60-kg body weight), respectively. Sodium picosulfate was not genotoxic in genotoxicity studies. Sodium picosulfate or PicoPrep was not teratogenic in rats and rabbits and did not have any adverse effect on fertility and early embryonic development in rats. In addition, sodium picosulfate was not genotoxic. Overall, nonclinical studies conducted with PicoPrep provide adequate assurance of safety and support its proposed use at the intended therapeutic dosage and in accordance with the proposed product labeling.

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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
05/14/2012

SUSHANTA K CHAKDER
05/14/2012

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 202535 | **Applicant: Ferring Pharmaceuticals, Inc.** | **Stamp Date: 9/16/11**

Drug Name: PicoPrep | **NDA Type: New NDA** | **Submit Date: 9/16/11**

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?	√		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	√		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	√		
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)?	√		
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).	√		
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?	√		
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?	√		

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
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	√		
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 will 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. _____**N/A**

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. November 1, 2011
Reviewing Pharmacologist Date

Sushanta K. Chakder, Ph.D. November 1, 2011
Supervisor Date

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

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
11/01/2011

SUSHANTA K CHAKDER
11/01/2011