CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-551

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-551
Brand Name (Proposed):	Half Lytely Bowel Prep
Generic Name:	PEG-3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution and bisacodyl enteric coated tablets
Dosage form and Strength:	Four 5 mg bisacodyl enteric coated tablets plus a white powder for reconstitution (210 g PEG-3350, 2.86 g sodium bicarbonate, 5.6 g sodium chloride, 0.74 g potassium chloride, and 1.0 g flavoring ingredient; if applicable)
Route of administration:	Oral
Indication:	For bowel cleansing prior to colonoscopy
Sponsor:	Braintree Lab. Inc.
Type of submission:	Original
Clinical Division:	Gastrointestinal and Coagulation Drugs (HFD-180)
OCPB Division:	HFD-870/DPE II
Priority:	Standard
Submission date:	08/15/02, 11/25/02 (N-000-BZ)
OCPB Consult date:	08/21/02
Reviewer:	Tien-Mien Chen, Ph.D.
Team leader:	Suresh Doddapaneni, Ph.D.

I. Executive Summary

PEG 3350 is an active ingredient of GoLytely® and NuLytely® currently on the market. It acts as an osmotic agent inducing diarrhea and thereby cleansing the bowel prior to colonoscopy. PEG 3350 has been reported to be minimally absorbed *in vivo* (<0.1%) and the absorbed PEG 3350 is mainly excreted unchanged in the urine.

Bisacodyl is a Category 1 OTC laxative agent formulated as an enteric coated 5 mg tablet for treatment of occasional constipation in a dose range of 5-15 mg for adults. A single administration of 20 mg has been reported for use in preparation of patients for surgery or for colonic X-Ray and endoscopic examination.

The sponsor is seeking approval for **Half Lytely® Bowel Prep** — under NDA 21-551 for bowel cleansing prior to colonoscopy. Each **Half Lytely® Bowel Prep** — consists of: **1)** four enteric coated 5 mg bisacodyl tablets and **2)** Half Lytely powder for reconstitution to 2 liters of solution containing 210 g polyethylene glycol 3350, electrolytes, and flavoring ingredient (if applicable). Half Lytely powder for reconstitution is exactly half that of NuLytely® currently on the market. When dissolved in water to a volume of 2 liters, Half Lytely solution is also isosmotic.

Four Half Lytely bisacodyl tablets (4 x 5mg) are to be administered orally to induce a bowel movement (occurs usually within 2-6 hrs) prior to administration of Half Lytely solution given orally as a gastrointestinal lavage. With administration of bisacodyl tablets, a reduction of PEG solution from 4 liters of 2 liters is expected to increase the compliance.

No new pharmacokinetic (PK) studies were conducted to support this NDA. However, two pivotal clinical trial data was submitted. Regarding dissolution data of bisacodyl enteric coated tablets, the rationale for selection of the dissolution method/parameters has not been provided. Significant drug-drug interaction (DDI) between bisacodyl and PEG 3350 is unlikely.

A. Recommendations

NDA 21-551 submitted on 08/15/02 by Braintree has been reviewed by OCPB/DPE II. OCPB is of the opinion that from clinical pharmacology and Biopharmaceutics perspective, the NDA is acceptable provided that the sponsor submits an adequate rationale for the dissolution method and a mutual understanding is reached with respect to package insert (PI) language. The OCPB recommendations need to be conveyed to the sponsor. Please see the labeling changes proposed by OCPB in Appendix 1 for details.

04/29/03
Tien-Mien Chen, Ph.D.
Division of Pharmaceutical Evaluation II

RD initialed by Suresh Doddapaneni, Ph.D. 05/07/03

FT initialed by Suresh Doddapaneni, Ph.D. 05/13/03

cc: NDA 21-551, HFD-180 (R. Prizont, A. Kacuba), HFD-870 (T. M. Chen, S. Doddapaneni, J. Hunt, H. Malinowski).

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III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

PEG 3350 has been shown to exhibit; **1)** no sign of *in vivo* metabolism and/or fermentation to hydrogen or methane by colonic flora, **2)** no detectable plasma levels after administration of PEG 3350, and **3)** a minimum of urinary excretion, 0.06 ± 0.01% in normal controls and 0.08 ± 0.02 % in patients with inflammatory bowel disease.

Bisacodyl is a prodrug. It is hydrolyzed by intestinal brush border enzymes and colonic bacteria to an active metabolite (BHPM) which causes peristalsis through a contact action on the luminal brush border. Both bisacodyl and BHPM are poorly water-soluble with reported minimal absorption from GI. The bisacodyl enteric coated tablet lots used in the pivotal clinical trials and for stability testing were manufactured by the sponsor.

The proposed mode of administration is four Half Lytely bisacodyl tablets (4 x 5 mg) administered orally to induce a bowel movement (occurs usually within 2-6 hrs) prior to administration of Half Lytely solution given orally as a gastrointestinal lavage.

No new PK data was submitted in this NDA. Dissolution data for 3 bisacodyl tablet lots using a modified USP method was submitted (bisacodyl delayed release tablet is a monograph in USP). The proposed dissolution and specifications should be used on an interim basis until an adequate rationale is provided for choosing conditions employed in the proposed method.

One supportive clinical trial (**F38-15**) compared **1)** bisacodyl tablets alone and **2)** 2 liters of NuLytely alone, and **3)** 4 liters of NuLytely. However, the results showed that either bisacodyl tablets alone or 2 liters of NuLytely alone was significantly inferior ($p<0.001$) to 4 liters of NuLytely. Subsequently, FDA suggested a classical 2x2 factorial design for a clinical study (and for DDI as well) comparing **1)** bisacodyl tablets alone, **2)** 2 liters of NuLytely alone, and **3)** a combination of bisacodyl tablets and 2 liters of NuLytely. However, the protocol was <u>not</u> approved by IRB due to ethical reasons, since treatments 1 and 2 were shown to be ineffective previously.

In the two pivotal clinical trials (**F38-13/14** and **F38-20**), 186 patients received the active treatment (proposed dosing regimen) and compared with 194 patients receiving the currently approved 4 liters of NuLytely®. Sponsor reported that no clinically significant differences in serum hematology, chemistries, electrolytes, or osmalality were observed, however, Half-Lytely reportedly showed significant improvement in patients' symptom profile and superiority in acceptability.

Upon OCPB request, the sponsor submitted on 11/25/02 (N-000, BZ) additional information/ reports to address DDI concerns between bisacodyl and PEG 3350 in order to support the above proposed dosing regimen.

IV. Question Based Review

A. General Attributes

Bisacodyl is classified under the proposed FDA OTC monograph system as a stimulant laxative for treatment of occasional constipation. An oral dose of 5-15 mg daily for adults is recommended. In addition, the professional labeling permits a single administration " for use in preparation of the patient for surgery or for preparation of the colon for X-ray and endoscopic examinations". NuLytely® (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution) approved under NDA 19-797 in 1991 is indicated for bowel cleansing prior to colonoscopy. For use, NuLytely® is to be reconstituted to 4 liters of volume and consumed at a rate of 240 mL every 10 minutes until the rectal effluent is clear or 4 liters are consumed. Because of the large volume of fluids and associated discomfort, patients may not fully comply with the regimen.

To improve compliance, Braintree Laboratories has developed the Half Lytely Bowel Prep System consisting of four 5 mg bisacodyl enteric coated tablets and half the amount of NuLytely®. The rationale is that the colonic purgation cannot be duplicated with each component used alone yet at the same time, it is an easier preparation to take for the patients. Patients are recommended to take all four bisacodyl tablets with water, wait for a bowel movement (or a maximum of 6 hours) then begin taking the PEG 3350 and electrolyte solution at a rate of 240 ml every 10 minutes, until the rectal effluent is clear or 2 liters are consumed. The day before the scheduled exam, patients are to consume clear liquids only (no solid food, no milk).

B. General Clinical Pharmacology

PEG 3350 acts as an osmotic agent which induces diarrhea and therefore cleanses the bowel prior to colonoscopy. Bisacodyl is an inactive prodrug that is hydrolyzed by intestinal brush border enzymes and colonic bacteria to an active metabolite (BHPM) which causes peristalsis through a contact action on the luminal brush border.

C. Extrinsic Factors

No new PK data was submitted to address the DDI potential between bisacodyl and PEG 3350 in order to support the above proposed dosing regimen.

Q: Could bisacodyl and PEG 3350 show significant DDI?

A: It is unlikely that bisacodyl and PEG 3350 would show significant DDI.

Although no PK study was conducted, additional information was submitted on 11/25/02 (N-000, BZ) to address the above DDI issue. Herve et al (2001) introduced PEG 3350 (10 g in 10 ml) and bisacodyl (10 mg in 10 ml) into subjects' colons 30 min apart with a randomized order of laxative administration in 6 constipated patients and 6 normal controls. The results showed PEG did not appear to have any effect on bisacodyl induced propagating contractions.

In another study by Sharma et al (2001), a 4-liter bowel preparation with PEG 3350 (GoLytely) given to 21 patients was compared with a 2-liter PEG 3350 preparation given simultaneously with 20 mg bisacodyl in 24 patients. No statistically significant changes in serum electrolytes, heart rates, arrhythmias, or hemodynamics measures were observed between two preparations.

Since the 20-mg dose of an enteric coated bisacodyl is to be given first to induce bowel movement (occurs usually 2-6 hrs) prior to administration of a 2-liter preparation of Half Lytely, a significant DDI is unlikely to occur.

Reference:

Herve et al: Effect of PEG 4000 ion 24-hr manometric recordings of left colonic motor activity. Eur. J. Gastro. & Hepatology 2001; 13: 647-654.

Sharma et al: The effect of stimulant laxatives and PEG lavage solution for colonoscopy preparation on serum electrolytes and hemodynamics. J. Clin. Gastroenterol. 2001; 32:238-239.

D. General Biopharmaceutics

Q: Is a food effect study needed for bisacodyl enteric coated tablet dosage form?

A: The food effect study is not needed.

Since the patients will be instructed the day before the scheduled exam to consume clear liquids only (no solid food, no milk), the food effect on the PK of bisacodyl is unlikely. Therefore, the food effect study is not needed.

Q: Is the proposed *in vitro* release test method and specifications for the bisacodyl enteric coated tablets adequate?

A: It is not clear as to how the sponsor chose the conditions of the dissolution method. Sponsor should provide adequate explanation supporting the above. The dissolution method and conditions are shown below and they should be used on an interim basis:

Apparatus:	**2 (paddle)**
Rotation:	**100 rpm**
Medium:	**98% SDS (0.02 M)/2.0% EtOH**
Volume:	**900 ml at 37± 0.5°C**
Sampling Time:	**10 min and 45 min**
Specifications:	**NMT − at 10 min and NLT _ . at 45 min**

According to USP 26 <701>, the procedure for disintegration testing is stated as follows: the tablets (n=6) in the chambers of apparatus were **1)** first immersed in simulated gastric fluid (SGF) at 37 ± 2°C for one hr (the tablets should show no evidence of disintegration) and **2)** tablets were then removed and immersed in simulated intestinal fluid (SIF): all of the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrated complete.

Dissolution:

Dissolution data of 3 stability batches (Lot Nos. 852, 853, and 854) were submitted for review. For the dissolution testing on each bisacodyl batch/lot, 12 tablets were tested and the mean (± standard deviation, SD) results that were obtained in the alkaline stage only are shown below: (no results in the acid stage were provided)

Mean (± SD) Dissolution Data of Bisacodyl Tablet Lots in SIF at 37 ± 2°C					
Lot No.	**10 Min**	**15 Min**	**30 Min**	**45 Min**	**60 Min**
852 (n=12)	0.8 ± 0.4	3.7 ± 6.1	77.0 ± 13.9	95.2 ± 1.0	95.8 ± 1.0
853 (n=12)	0.6 ± 0.6	4.6 ± 5.5	72.5 ± 25.2	96.3 ± 5.5	98.0 ± 4.0
854 (n=12)	0.6 ± 0.4	1.7 ± 2.9	79.9 ± 21.1	100.3 ± 2.9	100.7 ± 3.2

V. Labeling Recommendations

Detailed labeling recommendations are shown in Appendix 1. The OCPB labeling recommendations (underlined for addition and strikeout for deletion) should be conveyed to the sponsor.

VI. Appendices

1. Proposed Package Insert (Original with OCPB Recommendations)

2. OCPB Filing/Review Form

NDA 21-551 (Half Lytely Bowel Prep System)

Appendix 1

Sponsor's Proposed Labeling (08/02 version)

4 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

NDA 21-551 (Half Lytely Bowel Prep System)

Appendix 2

OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-551**	**Brand Name**	**Half Lytely**
OCPB Division (I, II, III)	**II**	**Generic Name**	**Polyethylene Glycol 3350**
Medical Division	**HFD-180**	**Drug Class**	
OCPB Reviewer	**Tien-Mien Chen, Ph.D.**	**Indication(s)**	**Bowl Cleansing**
OCPB Team Leader	**Suresh Doddapaneni, Ph.D.**	**Dosage Form**	**Powder for Oral Solution**
		Dosing Regimen	**Prior to Colonoscopy**
Date of Submission	**08/15/02**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**05/01/03**	**Sponsor**	**Braintree**
Medical Division Due Date	**05/15/03**	**Priority Classification**	**S**
PDUFA Due Date	**06/15/03**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE	[redacted]			[redacted]
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology	[redacted]			
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**Ref #12**			
multiple dose:				
Patients-				
single dose:	**Ref #2**			
multiple dose:				
Dose proportionality -				
Fasting / non-fasting single dose:				
Fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	**Ref #8, 16, 23, 26**			**No PK/PD analysis was done**

Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:	**Ref #4, 6**			**Bisacodyl PK in healthy volunteers (#4)**
Alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**8**		

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable. **The possible drug-drug-interaction (DDI) between bisacodyl and PEG 3350 should be addressed.**
QBR questions (key issues to be considered)	**Is there a PK and/or PD effect of bisacodyl on the PK of PEG 3350 or vice versa although each of them has been on the market?**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Tien-Mien Chen, Ph.D. 10/03/02**	
Secondary reviewer Signature and Date	**Suresh Doddapaneni, Ph.D. 10/03/02**	

CC: NDA 21-551, HFD-850 (Electronic Entry or Lee), HFD-180 (CSO), HFD-870 (T. M. Chen, S. Doddapaneni, H. Malinowski, J. Hunt), CDR (Z. Zadeng)

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/s/

Tien-Mien Chen
5/19/03 08:35:14 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
5/19/03 08:43:30 AM
BIOPHARMACEUTICS