OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 21551, S-013	Submission Date(s): 09/17/2009
Submission Type; Code	Clinical Efficacy Supplement
Brand Name	HalfLytely® and Bisacodyl Tablets Bowel Prep Kit
Generic Name and strength	PEG 3350 (210g), sodium chloride (5.6g), sodium bicarbonate (2.86g) and potassium chloride (0.74g) for oral solution (for reconstitution to 2 L), and 5-mg bisacodyl delayed-release tablet
Reviewers	Dilara Jappar, Ph.D.
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Gastroenterology Products
Sponsor	Braintree Laboratories, Inc
Proposed Indication	For bowel cleansing prior to colonoscopy
PDUFA Goal Date:	07/17/2010

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1 Executive Summary and Recommendation

1.1 Recommendation

The application is acceptable from a clinical pharmacology perspective provided that a mutual agreement regarding labeling language can be reached between the sponsor and Agency.

1.2 PMC/PMR

The following clinical pharmacology-related PMC/PMR are being requested from the sponsor:

Post Marketing Commitment (PMC):

Conduct a prospective, 3-arm trial evaluating HalfLytely with 5 mg bisacodyl, 2L polyethylene glycol solution plus electrolytes without bisacodyl, and 4L polyethylene glycol solution plus electrolytes without bisacodyl. The trial should evaluate the pharmacokinetics, efficacy and safety of each regimen in cleansing the colon as a preparation for colonoscopy in adults. Collect pharmacokinetic data in a subset of patients.

Post Marketing Requirements (PMR):

The sponsor has committed to conduct the following clinical pharmacology-related pediatric studies as PMR under PREA.

Study 2: A randomized, single-blind, multicenter dose-ranging study to obtain pharmacokinetic data and to compare the safety and efficacy of HalfLytely and Bisacodyl Tablet versus NuLYTELY in children (6 - 11 years of age).

Study 3 will be conducted if data from Study 2 supports evaluation of HalfLytely and Bisacodyl Tablet in younger pediatric subgroups.

Study 3: A randomized, single-blind, multicenter dose-ranging study to obtain pharmacokinetic data and to compare the safety and efficacy of HalfLytely and Bisacodyl Tablet versus NuLYTELY in children (birth - 5 years of age).

1.3 Regulatory Background

HalfLytely and Bisacodyl Tablets Bowel Prep Kit [PEG 3350 powder, electrolytes, and 20 mg (four 5 mg) enteric coated bisacodyl tablets] under NDA 21551 was approved on 05/10/04 for the indication of bowel cleansing prior to colonoscopy. Due to post-marketing reports of abdominal cramping and ischemic colitis associated with the HalfLytely kit use containing 20 mg bisacodyl, the sponsor submitted Supplement S-006 to reduce the dose of bisacodyl in the kit from 20 mg to 10 mg (from four tablets to two 5 mg enteric coated bisacodyl tablet). The supplement was approved on September 24, 2007. In the supplement approval letter, FDA requested that additional studies be performed to evaluate lower doses of bisacodyl. In particular, FDA suggested that doses of 7.5, 5 mg and/or 2.5mg bisacodyl be evaluated. Braintree clinical protocol F38-27, presented in the current supplement, was subsequently developed to evaluate if a HalfLytely kit containing a dose of 5 mg bisacodyl would be as effective as the approved kit containing 10 mg bisacodyl. This protocol was submitted to the FDA on December 28, 2007.

The active ingredients of this kit have been in the market for some time. PEG 3350 is an active ingredient of GoLytely and NuLytely and it acts as an osmotic agent inducing diarrhea and cleans

the bowel prior to colonoscopy. Bisacodyl is a Category I OTC monograph laxative agent formulated as an enteric-coated 5-mg tablet for treatment of occasional constipation in the dose range of 5-15 mg for adults.

1.4 Submission Contents

On 09/17/09, the sponsor (Braintree) submitted a clinical efficacy supplement under SE-013 with new clinical efficacy data to support the reduction of bisacodyl dose in the HalfLytely and Bisacodyl Tablets Bowel Prep Kit from 10 mg (2 tablets) to 5 mg (1 tablet). There were no changes to the formulation other than reducing the number of bisacodyl tablets in the Kit from two to one.

The sponsor did not submit any new human pharmacokinetic (PK) or clinical pharmacology studies under this Supplement SE-013. However, we have several labeling recommendations for section 12 of PI that is related to clinical pharmacology.

2 Detailed Labeling Recommendations

Reviewer's recommended addition is shown with an underline and deletion is shown with ~~strikethrough line~~

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

~~HalfLytely and Bisacodyl Tablet Bowel Prep Kit induces diarrhea which cleanses the colon.~~

Polyethylene glycol (PEG), which is an osmotic agent, causes water to be retained within the gastrointestinal tract.

Bisacodyl is hydrolyzed by intestinal brush border enzymes and colonic bacteria to form an active metabolite [bis-(p-hydroxyphenyl) pyridyl-2 methane; (BHPM)] that acts directly on the colonic mucosa to produce colonic peristalsis.

12.2 Pharmacodynamics

~~Bisacodyl, a stimulant laxative, is hydrolyzed by intestinal brush border enzymes and colonic bacteria to form an active metabolite [bis-(p-hydroxyphenyl) pyridyl-2 methane; (BHPM)] that acts directly on the colonic mucosa to produce colonic peristalsis.~~

The stimulant laxative effect of bisacodyl, together with the osmotic effect of the unabsorbed PEG when ingested with a large volume of water, produces watery diarrhea.

12.3 Pharmacokinetics

~~The osmotic activity of HalfLytely solution results in no net absorption or excretion of ions or water.~~

When taken orally, PEG 3350 is minimally absorbed.

Bisacodyl, which is a prodrug, is converted to its active metabolite BHPM by intestinal brush border enzymes and colonic bacteria.

Comment for sponsor:
Please add bisacodyl ADME information in section 12.3.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21551	SUPPL-13	BRAINTREE LABORATORIES INC	HALF LYTELY BISACODYL BOWEL PREP KIT

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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06/30/2010

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06/30/2010

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07/01/2010