CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-551

PHARMACOLOGY REVIEW(S)

3 Page(s) Withheld

1 § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-551

Review number: 1

Sequence number/date/type of submission: 000/August 15, 2002/Original

Information to sponsor: Yes ( ) No ( )

Sponsor and/or agent: Braintree Laboratories, Inc., Braintree, MA.

Manufacturer for drug substance:

a. Polyethylene Glycol 3350, NF: —

b. Electrolyte salts (sodium bicarbonate, USP; sodium chloride USP; potassium chloride USP): —

c. Bisacodyl, USP: —

Reviewer name: Tamal Chakraborti, Ph.D.

Division name: Gastrointestinal and Coagulation Drug Products

HFD #: 180

Date of Receipt by FDR/CDER: August 19, 2002

Review completion date: November 13, 2002

Drug:

Trade name: HalfLytely®

Generic name: Polyethylene Glycol (PEG)-3350, Sodium Chloride, Sodium Bicarbonate, Potassium Chloride for Oral Solution and Bisacodyl Tablets

Code name: None

Chemical name: Polyethylene Glycol (PEG)-3350, Sodium Chloride, Sodium Bicarbonate, Potassium Chloride for Oral Solution and Bisacodyl [4,4'-(2-pyridylmethylene) bisphenoldiacetate]

CAS registry number: Not provided

Mole file number: Not available

Molecular formula/molecular weight:

Polyethylene Glycol 3350: $H(OCH_2CH_2)_nOH/3350$ (approximate)
Sodium Chloride: NaCl/58.45
Sodium Bicarbonate: $NaHCO_3/84.00$
Potassium Chloride: KCl/74.55
Bisacodyl USP: $C_{22}H_{19}NO_4/361.38$

Relevant INDs/NDAs:

1. IND 57, 673 (HalfLytely, Braintree Laboratories, Inc.)
2. NDA 19-797 (NuLytely, Braintree Laboratories, Inc.)
3. NDA 19-011 (GoLytely, Braintree Laboratories, Inc.)

Drug class: Laxative

Indication: HalfLytely is indicated for bowel cleansing prior to colonoscopy.

Clinical formulation: The composition and dosage form is shown below (from Vol. 1.1., page 14 of sponsor's submission).

5.2.1 *Composition and Dosage Form*

Each dose of Half Lytely consists of one 2L jug of NuLYTELY with 4 Bisacodyl

Tablets 20 mg (5 mg each)

5.2.2 *Half Lytely Solution*

Each dose contains (grams per 2 liter container):

Polyethylene Glycol 3350, NF	210	g
Sodium Chloride, USP	5.60	g
Sodium Bicarbonate, USP	2.86	g
Potassium Chloride, USP	0.74	g
Flavor Ingredients (optional)	1.00	g
Cherry Flavor		
Lemon-Lime Flavor		
Orange Flavor		

Route of administration: Oral

Proposed use: HalfLytely is intended to be used for bowel cleansing prior to colonoscopy.

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

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Executive Summary

I. Recommendations

A. Recommendation on Approvability: From a preclinical standpoint, this NDA may be approved.

B. Recommendation for Nonclinical Studies: None.

C. Recommendations on Labeling: Sponsor should be asked to change the proposed label of HalfLytely Bowel Prep — as suggested in the text of the review.

II. Summary of Nonclinical Findings

A. Pharmacological Activity: The pharmacological properties of the components of HalfLytely Bowel Prep — were well characterized and evidenced in several scientific publications. Bisacodyl, a diphenylmethane derivative, is a stimulant laxative, which exerts its action primarily through stimulation of mucosal nerve plexus in the colon resulting in the contractions of the entire colon. NuLYTELY (a combination of PEG 3350, sodium chloride, sodium bicarbonate and potassium chloride) is a combination of saline and osmotic laxatives. Saline laxatives (sodium chloride, sodium bicarbonate and potassium chloride) generally act by their osmotic pressure to retain water in the colon. The osmotic laxatives (PEG 3350) are poorly absorbed and are resistant to digestion in the small intestine. The large volume of non-absorbable fluid results in copious watery diarrhea and the efficient removal of solid wastes from the gastrointestinal (GI) tract.

B. Brief Overview of Toxicology: The sponsor did not conduct any preclinical toxicology study with HalfLytely. In a 3-Day oral gavage study in beagle dogs with Vet-Prep (Polyethylene Glycol/Electrolyte Solutions or PEG-ELS for veterinary use of PEG-ELS) at 15.8 g/kg/day, PEG-ELS did not produce any signs of toxicity except soft stools and diarrhea. In acute toxicity studies with bisacodyl in rats and mice, the oral LD_{50} values of bisacodyl were determined as 4.32 and 17.5 g/kg, respectively. In a chronic (44 weeks) oral (through diet) toxicity study with bisacodyl in rats at 0, 1.2, 6 and 30 mg/kg/day, bisacodyl did not produce any significant organ toxicity. In a chronic (44 weeks) oral (through diet) toxicity study with in beagle dogs at 0, 0.75, 4.175 and 20.8 mg/kg/day, bisacodyl did not produce any sign of toxicity.

C. Nonclinical Safety Issues Relevant to Clinical Use: The safety of the PEG and electrolyte components in Halflytely is well established through its clinical and postmarketing experience. Bisacodyl is also approved (non-prescription drug) as a Category I OTC laxative at a dose of 5 to 15 mg/day. In addition, the proposed single dose of 20 mg of bisacodyl, when used as part of a bowel cleansing regimen is also within the limit described in 21 CFR 334.66(d)(3)(iii)(a). Therefore, from a preclinical standpoint, there is no safety concern for the proposed use of Halflytely Bowel Prep —

III. Administrative

A. Reviewer signature: _____

B. Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

C. cc: list:

Original NDA
HFD-180
IND 57, 673
HFD-180
HFD-181/CSO
HFD-180/Dr. Chakraborti
HFD-180/Dr. Choudary
HFD-045/Dr. Viswanathan

R/D Init. J Choudary: November 11, 2002
TC/tc: November 13, 2002
C:\DATA\PHARM\N\21551.02.10.0TC

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PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

The pharmacological properties of the components of HalfLytely Bowel Prep — were well characterized and evidenced in several scientific publications. Bisacodyl, a diphenylmethane derivative, is a stimulant laxative, which exerts its action primarily through stimulation of mucosal nerve plexus in the colon resulting in the contractions of the entire colon. NuLYTELY (a combination of PEG 3350, sodium chloride, sodium bicarbonate and potassium chloride) is a combination of saline and osmotic laxatives. Saline laxatives (sodium chloride, sodium bicarbonate and potassium chloride) generally act by their osmotic pressure to retain water in the colon. The osmotic laxatives (PEG 3350) are poorly absorbed and are resistant to digestion in the small intestine. The large volume of non-absorbable fluid results in copious watery diarrhea and the efficient removal of solid wastes from the gastrointestinal (GI) tract.

II. SAFETY PHARMACOLOGY: NONE

III. PHARMACOKINETICS/TOXICOKINETICS:

The sponsor did not submit any pharmacokinetic study with HalfLytely. The published report has been (Roth W and Beschke K. *Drug Research* 1988; 38: 570 – 574) reviewed below.

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ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION:

Pharmacokinetics and Laxative Effect of Bisacodyl after Administration of Different Preparation Forms (Drug Research 38: 570-574, 1988).

Methods: The pharmacokinetics of Bisacodyl were evaluated in 12 human subjects (6 males and 6 females), which received 10 mg of drug either orally in a 0.05 M aqueous hydrochloric acid solution (pH 1.7), orally with an enteric coated tablet (Ducolax®), or rectally in suppository form. This 10 mg dose, for a 50 kg person, is equivalent to 0.2 mg/kg. The enteric coated tablet is resistant to stomach gastric juices, and dissolves in the lower sections of the intestine. The three formulations were given on separate days with a 3-4 day washout period between studies. For each formulation, blood was collected at time points between 0 and 24 hr following administration. Urine was collected from 0-10 hr in 2 hr intervals, 10-24 hr, and 24-48 hr. Plasma and urinary drug levels were determined by chromatographic detection of the glucuronide conjugate of the diphenol form of bisacodyl. The active laxative agent is the diphenol form of bisacodyl (bis-(p-hydroxyphenyl)-pyridyl-2-methane), which is formed from hydrolysis of bisacodyl. The diphenol form is rapidly conjugated with glucuronic acid. The onset of the laxative effect for each formulation was determined.

Results: Following oral administration of the solution, bisacodyl was quickly absorbed from the upper small intestine and rapidly attained a C_{max} of 237 ng/mL within 1.7 hr; however, the onset of the laxative effect did not occur until 5-7 hr after dosing. Following administration of enteric coated tablets, a C_{max} of 26 ng/mL was attained at 8 hr. Systemic bioavailability with enteric tablets ranged from 16-21% based upon AUC and urinary excretion data. Bioavailability with the solution and suppositories were not provided; however, it would be expected to be high with the solution and low with the suppositories. The C_{max} and T_{max} values for the suppository form were not calculated, because plasma drug levels were below detection limits; however, the laxative effect was evident within 20 min. Following administration of bisacodyl orally in a solution or rectally with a suppository, there was no connection between plasma drug levels and pharmacological effect.

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With the oral enteric tablets or suppository, the systemic absorption of bisacodyl in the large intestine is low, thus a higher drug concentration should be present in this area to exert a pharmacological effect. Plasma AUC data and fecal excretion were not provided for each of three formulations.

Pharmacokinetic of bisacodyl in three formulations (Adapted from table supplied with the submission).

Formulation	Dose of Bisacodyl (mg)	Plasma C_{max} (ng/mL)	Plasma T_{max} (hr)	Urine excretion (mg)
Enteric Tablet	10	26	8	0.9 (9% of dose)
Suppository	10	0-64[a]	-[a]	0.3 (3% of dose)
Solution	10	237	1.7	4.3 (43% of dose)

a. The C_{max} and T_{max} values for the suppository form were not calculated, because plasma drug levels were below detection limits.

IV. GENERAL TOXICOLOGY:

HalfLytely

The sponsor did not submit any preclinical toxicology study reports with HalfLytely. A 3-day oral toxicity study with Vet-Prep/PEG 3350 (HLA 2457-100) in beagle dogs was submitted under NDA 19-797 dated February 29, 1988. This study was previously reviewed under the above NDA 19-797. The review of this study is reproduced from the pharmacology review of NDA 19-797 dated April 28, 1989.

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3-Day Oral Toxicity Study in the Dogs
(Project # - 2457-100)

Conducting Lab:
Dates of Conduct: Initiated April 6, 1987, completed April 9, 1987
GLP Statement: In compliance with FDA's GLPs.

MATERIALS AND METHODS

Chemical: PEG 3350, Vet-Prep; lot # 70232 in distilled water.
Animals: Beagle dogs, 6-8 kg males, and 4-6 kg females; 3/sex/group
Doses: 0 (control vehicle) and 26.4 ml/kg/10 hours (=15.8 g/kg/d).

Methods: The dogs were given the test substance or control vehicle by gavage once every hour for 10 hours daily for 3 days. The animals were observed daily for morbidity; the body weights, food and water consumption were recorded initially and daily for 3 days. Hematology, clinical chemistry and ophthalmology were also recorded. However, the frequency of blood collection was not mentioned. At termination, all the animals were sacrificed and necropsied. The tissues/organs were weighed and examined macro- and microscopically.

Results: There were no deaths. All drug-treated dogs had soft stools and diarrhea during the treatment.

There were no significant drug-related changes in body weights, ophthalmic examinations, food consumption, clinical chemistry (including SGOT, SGPT, total bilirubin, BUN, serum creatinine and serum osmolality), hematology (including platelets), organ weights (except kidneys, see below).

Organ weights: The absolute kidney weights in the treated male dogs were higher ($p < 0.05$) than the controls (42.3 v/s 47.1 g) but not in the females (36.4 g in the treated v/s 35.4 g in the control dogs). The relative weights did not seem to differ significantly (males 0.60 v/s 0.70, and females 0.68 v/s 0.73).

Histopathology: There were no remarkable histological changes in any organ.

In summary, PEG-3350 tested at 15.8 g/kg/d for 3 days produced no significant toxicity in the beagle dogs except soft stools and diarrhea.

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Bisacodyl

The published reports of acute toxicity studies with bisacodyl in mice, rats and dogs and chronic toxicity studies in rats and dogs (*Toxicology and Applied Pharmacology* 2: 243- 253, 1960) have been reviewed below.

TOXICOLOGY:

Acute Toxicity:

Mice, Rats, and Dogs

Studies on the Toxicity of 2-(4,4'-diacetoxydiphenylmethyl)pyridine (Toxicology and Applied Pharmacology 2: 243-253, 1960).

Methods: The acute toxicity of bisacodyl was evaluated in mice, rats, and dogs. Rats and mice were administered bisacodyl by the intragastic route. The vehicle was a 1% aqueous solution of Polysorb 80. Animals were monitored over a 14 day period following drug administration. The acute intravenous toxicity of bisacodyl was assessed in mice and propylene glycol was used as the vehicle. Acute toxicity studies with dogs were difficult, because animals regurgitated the higher doses. It was necessary to treat the dogs with Thorazine, and administer bisacodyl using a stomach tube in divided doses over a 24 hr period. Dogs were monitored over a 7 day period.

Results: In acute toxicity tests, the oral LD_{50} values for rats and mice were 4.32 and 17.5 g/kg, respectively. For rats at doses > 4.10 g/kg, toxic signs included abdominal distress, laxation, and prostration. For mice at doses ≥ 16.34 g/kg, incoordination, convulsions, and accelerated respiration were observed. The

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intravenous LD_{50} value for mice was 0.096 g/kg. No deaths occurred with dogs receiving bisacodyl at doses ranging from 9.2 to 15.0 g/kg.

Acute Toxicity of Bisacodyl in Mice, Rats, and Dogs

Species	Route	Dosage g/kg	LD_{50} g/kg	Highest nonlethal dose g/kg	Minimum lethal dose g/kg
Mice	Oral	8.19, 16.34, 32.77	17.5	8.19	16.34
Mice	Intra-venous	0.04, 0.08, 0.112, 0.160	>0.096[a]	0.040	0.080
Rat	Oral	2.05, 4.10, 8.19, 16.38	4.32	< 2.05	2.05
Dog	Oral	9.2-15.0	Not determined	> 15.0	–

a. Propylene glycol, the vehicle used for intravenous administration of bisacodyl, at dose volumes of 4, 6, and 8 mL/kg caused 0, 10, and 80% mortality. The dose volumes for 0.112 and 0.160 g/kg bisacodyl were 5.7 and 8.0 mL/kg, respectively, while 0.040 and 0.080 g/kg were < 4.0 mL/kg.

Chronic Toxicity:

Studies on the Toxicity of 2-(4,4'-diacetoxydiphenylmethyl)pyridine (Toxicology and Applied Pharmacology 2: 243-253, 1960).

Methods: The chronic toxicity of bisacodyl was evaluated in rats and dogs: Rats received bisacodyl in the diet at concentrations of 0, 0.002, 0.01, or 0.05% for periods up to 44 weeks. Estimated dosages are 0, 1.2, 6, and 30 mg/kg/day, respectively. There were 20 animals/sex/group. Beagles received bisacodyl in the diet at concentrations of 0, 0.003, 0.0167, or 0.0833% for periods up to 44 weeks. Estimated dosages are 0.75, 4.175, and 20.8 mg/kg/day, respectively. There were 6 dogs/sex/group. Body weight, food consumption, and hematological parameters were monitored in rat and dog studies. At selected treatment intervals, animals were sacrificed and necropsy examinations were performed. Organ weights were measured. Histopathological analysis was performed for rats and dogs of the high dose groups.

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Results:

1. **Rat Study:** During the treatment period, stools for the 6 mg/kg/day group were soft, while those for the 30 mg/kg/day group were fluid. At the end of the 44 week treatment period, body weight gains for the male and female control groups were 369.8 and 207.2 grams, respectively. Weights gains for the male 1.2, 6, and 30 mg/kg/day groups were reduced to 96.9, 88.3, and 72.6% of the control, respectively. Body weight gains for the female 1.2, 6, and 30 mg/kg/day groups were reduced to 84.3, 80.2, and 76.3% of the control, respectively. Apparent treatment-related differences were observed for the Differential white cell count, as noted below; however, standard deviation values were not provided and the authors interpreted these findings as normal. The percentage neutrophils for the male 1.2, 6, and 30 mg/kg/day groups were increased to 138.9, 155.3, and 207.9% of the control (19%), respectively. Immature neutrophils for the male 1.2, 6, and 30 mg/kg/day groups were increased to 325, 214.3, and 228.6% of the control (2.8%), respectively. Lymphocytes for the male 1.2, 6, and 30 mg/kg/day groups were reduced to 83.1, 84.1, and 82.1% of the control (76.2%), respectively. No control changes in differential white cell counts were reported for female treatment groups. No treatment related differences were found with the pathological examination or organ weight determination. No histopathological changes were found for rats treated with 30 mg/kg/day.

2. **Dog study:** No changes in stool composition were observed for dog treatment groups. There were no treatment related changes in body weight gain, food consumption, or hematological parameters. After 23 weeks of treatment, 3 dogs from each group were sacrificed. No gross pathological changes were found in dogs from any treatment group. No histopathological changes were found for dogs treated with 20.8 mg/kg/day. Treatment periods prior to measurements were not precisely described.

Rats received bisacodyl in the diet at doses of 0, 1.2, 6, and 30 mg/kg/day for periods up to 44 weeks. Beagles received bisacodyl in the diet at doses of 0, 0.75, 4.175, and 20.8 mg/kg/day for periods up to 44 weeks. The no effect dose for rats was 1.2 mg/kg/day. The no effect dose for dogs appeared to be 20.8 mg/kg/day. There were no target organs of toxicity. A dose-related increase of the percentage neutrophils was observed for male rat treatment groups; although no changes were observed for female treatment groups. Impairment of weight gain was found for male and female rats receiving 6 and 30 mg/kg/day; however, no changes were found with dogs.

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V. GENETIC TOXICOLOGY:

The sponsor did not conduct any genetic toxicity study with HalfLytely.

VI. CARCINOGENICITY:

The sponsor did not conduct any carcinogenicity study with HalfLytely. However, the sponsor presented literature references regarding carcinogenicity studies with bisacodyl.

Bisacodyl was tested at 4.3 and 43 mg/kg (intragastric gavage) for its effects on azoxymethane (AOM)-induced aberrant crypt foci (ACF) and tumors in Wistar rats. Animals, divided in 10 groups were treated with AOM and bisacodyl (alone or in combination) for 13 weeks. At the end of treatment animals were killed and the colon removed and analyzed for the determination of ACF and tumors. Bisacodyl (4.3 and 43 mg/kg), given alone, did not induce the development of colonic ACF and tumors. Bisacodyl (4.3 mg/kg) coupled with AOM increased the number of crypt per focus, but not the number of tumors. Bisacodyl (43 mg/kg) significantly increased the number of crypt per focus and tumors. The results of the present study indicated a possible promoting effect of bisacodyl on rat colon carcinogenesis (especially at higher doses).

An *in vivo* study in rats was performed to compare the short- and long-term effect of bisacodyl on epithelial cell proliferation in the ileum and large intestine. Cell proliferation was examined by the bromodeoxyuridine (BrdUrd) labeling technique after 2, 6 and 12 weeks of continuous treatment. Treatment with bisacodyl did not induce any statistically significant increase of the labeling index (LI) when compared with the control group. The proliferative pattern along the crypts remains unchanged with bisacody throughout the study. In this study, bisacodyl did not appear to have any major influence on ileal and colonic epithelial cell proliferation.

Male and female rats were administered bisacodyl-diets at concentrations of 0.3, 0.1, and 0.03% (225, 75, 22.5 mg/kg/day, based on an average body weight of 200 g and an average food consumption of 15 g/animal/day) for 32 weeks. In this study, both sexes of bisacodyl-treated animals suffered from diarrhea throughout the experimental period. Epithelial proliferative lesions and calculus formation were observed only in the urinary bladder of male rats given the 0.3% bisacodyl diet. Proliferative lesions and increases of bromouracil deoxyriboside (BUdR) labeling indices were found only in the urinary bladder epithelium of rats with calculi. The severity of the proliferative lesions correlated with the calculus weight. These findings indicated a possible close relationship between the development of proliferative lesions and the existence of calculi in the urinary bladder. The results of this study suggested that bisacodyl-induced proliferative lesions are probably not caused directly by bisacodyl per se but are secondary to calculus formation.

In a 26-week carcinogenicity study in p53 (+/-) transgenic mice, bisacodyl did not show any carcinogenic potential at doses up to 8000 mg/kg/day.

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY: NONE

VIII. SPECIAL TOXICOLOGY STUDIES: NONE

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LABELING: The draft labeling of HalfLytely Bowel Prep — conforms to the format specified under CFR 21, subpart B, 201.5 to 201.57 dated April, 1998. However, the following changes should be made in the proposed labeling:

Proposed Labeling:

1. **Carcinogenesis, Mutagenesis, Impairment of Fertility:**

Sponsor's Version:

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Reviewer's Comments: The text should be modified as stated below.

Recommendation: The proposed text of sponsor should be modified as stated below:

Carcinogenesis, Mutagenesis, Impairment of Fertility: "Long-term studies in animals have not been performed to evaluate the carcinogenic potential of HalfLytely Bowel Prep — Studies to evaluate its potential for impairment of fertility or its mutagenic potential have not been performed."

2. **Pregnancy, Teratogenic Effects:**

Sponsor's Version:

Pregnancy: Category C. Animal reproduction studies have not been conducted with Half Lytely Bowel Prep — . *It is* also not known whether Half Lytely Bowel Prep — can cause fetal harm when administered to a *pregnant* woman or can affect reproductive capacity. Half Lytely Bowel Prep — should be given to a pregnant or nursing woman only if —

Reviewer's Comments: According to CFR 21, subpart B, 201.5 to 201.57, the subsection "Pregnancy. Teratogenic Effects." should be incorporated in the labeling.

Recommendation: The proposed text of sponsor should be modified as stated below:

"Pregnancy. Teratogenic Effects. Pregnancy Category C: Animal reproduction studies have not been conducted with HalfLytely Bowel Prep — It is also not known whether HalfLytely Bowel Prep — can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. HalfLytely Bowel Prep — should be given to a pregnant woman only if clearly needed."

3. **Nursing Mothers:**

Sponsor's Version: This section is missing in the draft labeling.

Reviewer's Comments: The sponsor should incorporate this section in the labeling.

Recommendation: The following text should be incorporated in the labeling as stated below:

"**Nursing Mothers:** It is not known whether HalfLytely Bowel Prep — is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when HalfLytely Bowel Prep — is administered to a nursing woman."

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IX. SUMMARY AND EVALUATIONS:

Braintree Laboratories has developed a low volume orthograde intestinal "lavage" regimen that is named as either "2 Liter NULYTELY plus Bisacodyl" or "2L+bis". The proposed trade name and generic name is Half Lytely® (PEG-3350, Sodium Chloride, Sodium Bicarbonate, Potassium Chloride for Oral Solution and Bisacodyl Tablets). When taken orally, 20 mg of bisacodyl followed by 2L of a solution containing polyethylene glycol 3350/Electrolyte salts (SF-ELS, identical to NuLytely® in composition), produces a voluminous bowel movement and watery diarrhea, which together cleanse the bowel prior to colonoscopy. In comparison to PEG based lavage solutions, which require the patient to consume 4L of solution, the reduced volume (2L) preparation significantly reduces patient symptoms associated with the larger volume preps without affecting bowel cleansing capability.

Bisacodyl, a diphenylmethane derivative, is a stimulant laxative, which exerts its action primarily through stimulation of mucosal nerve plexus in the colon resulting in the contractions of the entire colon. NuLYTELY (a combination of PEG 3350, sodium chloride, sodium bicarbonate and potassium chloride) is a combination of saline and osmotic laxatives. Saline laxatives (sodium chloride, sodium bicarbonate and potassium chloride) generally act by their osmotic pressure to retain water in the colon. The osmotic laxatives (PEG 3350) are poorly absorbed and are resistant to digestion in the small intestine. The large volume of non-absorbable fluid results in copious watery diarrhea and the efficient removal of solid wastes from the gastrointestinal (GI) tract.

General Toxicology Issues: The sponsor did not conduct any preclinical toxicology study with HalfLytely. However, a 3-Day study with Vet-Prep (Polyethylene Glycol/Electrolyte Solutions or PEG-ELS for veterinary use of PEG-ELS) was included in this submission. The sponsor did not submit any preclinical study with bisacodyl. However, preclinical studies [ADME (Roth W and Beschke K. *Drug Research* 1988; 38: 570 – 574) and acute toxicity studies in mice, rats and dogs and chronic toxicity studies in rats and dogs (*Toxicology and Applied Pharmacology* 2: 243- 253, 1960)] with bisacodyl are available in the published literature. In addition, the sponsor cited literature references regarding the acute and chronic individual toxicity studies with polyethylene glycol (PEG) and bisacodyl.

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

In acute toxicity studies with bisacodyl in rats and mice, the oral LD_{50} values of bisacodyl were determined as 4.32 and 17.5 g/kg, respectively. The intravenous LD_{50} of bisacodyl for mice was determined to be 0.096 g/kg. Bisacody was found to be nonlethal to dogs at doses ranging from 9.2 to 15.0 g/kg.

In a chronic toxicity study with bisacodyl in rats, animals were administered bisacodyl at the doses of 0, 0.002, 0.1 or 0.05 % (0, 1.2, 6 and 30 mg/kg/day) through diet for 44 weeks. A dose of 1.2 mg/kg/day was considered as a NOEL (no observed effect level). No histopathological

changes were observed up to 30 mg/kg/day. Target organ of toxicity could not be identified in the absence of any histopathological findings.

In a chronic toxicity study in beagle dogs, bisacodyl was given in diet at the doses of 0, 0.003, 0.0167 or 0.0833 % (0, 0.75, 4.175 and 20.8 mg/kg/day) for 44 weeks. No changes in stool composition, body weight gain, food consumption or hematological parameters were reported. No gross pathological or histopathological changes were seen at any of the tested doses. A dose of 20.8 mg/kg/day was considered as NOEL. The tested doses did not allow the identification of any target organ of toxicity.

The sponsor did not conduct any genotoxicity or carcinogenicity study with HalfLytely. However, the sponsor presented literature references regarding carcinogenicity studies with bisacodyl.

Bisacodyl was tested at 4.3 and 43 mg/kg (intragastric gavage) for 13 weeks for its effects on azoxymethane (AOM)-induced aberrant crypt foci (ACF) and tumors in Wistar rats. Bisacodyl (4.3 and 43 mg/kg), given alone, did not induce the development of colonic ACF and tumors. Bisacodyl (4.3 mg/kg) coupled with AOM increased the number of crypt per focus, but not the number of tumors. Bisacodyl (43 mg/kg) significantly increased the number of crypt per focus and tumors. The results of the present study indicated a possible promoting effect of bisacodyl on rat colon carcinogenesis (especially at higher doses).

An *in vivo* study in rats was performed to compare the short- and long-term effect of bisacodyl on epithelial cell proliferation using bromodeoxyuridine (BrdUrd) labeling technique in the ileum and large intestine. Treatment with bisacodyl did not induce any statistically significant increase of the labeling index (LI) when compared with the control group. The proliferative pattern along the crypts remains unchanged with bisacody throughout the study. Bisacodyl did not appear to have any major influence on ileal and colonic epithelial cell proliferation.

Male and female rats were administered bisacodyl-diets at concentrations of 0.3, 0.1, and 0.03% (225, 75, 22.5 mg/kg/day, based on an average body weight of 200 g and an average food consumption of 15 g/animal/day) for 32 weeks. Proliferative lesions and increases of bromouracil deoxyriboside (BUdR) labeling indices were found only in the urinary bladder epithelium of rats with calculi. These findings indicated a close relationship between the development of proliferative lesions and the existence of calculi in the urinary bladder. The results of this study suggested that bisacodyl-induced proliferative lesions might not be caused directly by bisacodyl per se but could be secondary to calculus formation.

In a 26-week carcinogenicity study in p53 (+/-) transgenic mice, bisacodyl did not show any carcinogenic potential at doses up to 8000 mg/kg/day.

Conclusions: From a preclinical standpoint, this submission satisfies the criteria for marketing authorization of HalfLytely Bowel Prep — and appears to be safe for the proposed use.

The present application seeks approval for the oral use of 20 mg of bisacodyl with 2 L of PEG-electrolyte solution (Nulytely) for bowel cleansing before colonoscopy. HalfLytely and Nulytely (approved under NDA 19-797) have identical concentrations of components; however, the latter

is presented in a 2-liter dose form. The safety of the PEG and electrolyte components in Halflytely is well established through its clinical and postmarketing experience. Bisacodyl is also approved (non-prescription drug) as a Category I OTC laxative at a dose of 5 to 15 mg/day. In addition, the proposed single dose of 20 mg of bisacodyl, when used as part of a bowel cleansing regimen is also within the limit described in 21 CFR 334.66(d)(3)(iii)(a). Therefore, from a preclinical standpoint, there is no safety concern for the proposed use of Halflytely Bowel Prep — This submission satisfies the criteria for marketing authorization of HalfLytely Bowel Prep — and appears to be safe for the proposed use.

The labeling of HalfLytely Bowel Prep — conforms to the format specified under CFR 21, Subpart B, 201.50-201.57 dated April, 1998. However, the suggested changes described in the text, should be incorporated.

Recommendations:

1. From a preclinical standpoint, this NDA may be approved.

2. Sponsor may be asked to change the proposed label of HalfLytely Bowel Prep — as suggested in the text of the review.

X. APPENDIX/ATTACHMENTS: NONE

Addendum to review: None

Other relevant materials: None

Any compliance issues: None

Signature:

Tamal K. Chakraborti, Ph.D. Date
Pharmacologist, HFD-180

Comment:

Jasti B. Choudary, B.V. Sc., Ph.D. Date
Supervisory Pharmacologist, HFD-180

cc:

Original NDA
HFD-180
IND 57, 673
HFD-180
HFD-181/CSO
HFD-180/Dr. Chakraborti
HFD-180/Dr. Choudary
HFD-045/Dr. Viswanathan

R/D Init. J Choudary: November 11, 2002
TC/tc: November 13, 2002
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/s/

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