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InKine Pharmaceutical Company, Inc.

MARTIN ROSE, M.D., J.D.
*Senior Vice President
Clinical Research & Regulatory Affairs*

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April 27, 2000

Dockets Management Branch
United States Food and Drug Administration
HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Re: Docket No. 78N-036L

Dear Madam or Sir:

I am writing on behalf of InKine Pharmaceutical Co., Inc (InKine), in response to a letter to Lilia Talarico, M.D., from Jack DiPalma, M.D., dated December 10, 1999. In that letter, Dr. DiPalma raised concerns about the safety of sodium phosphate bowel preparation products. The letter was placed on FDA's Dockets Web site (Docket No. 78N-036L) and is now available to the public. InKine is the manufacturer of Diacol™ Tablets (sodium phosphate monobasic, monohydrate and sodium phosphate dibasic, anhydrous), an investigational colon cleansing agent. We have several serious concerns regarding Dr. DiPalma's letter:

- We disagree strongly with Dr. DiPalma's conclusions regarding the risks of sodium phosphate products. His views are contrary to FDA's own published conclusions regarding the excellent safety record of sodium phosphate when it is used as directed.
- Dr. DiPalma failed to disclose his conflict of interest arising out of his role as a "medical director/consultant" of Braintree Laboratories, Inc (Braintree), a manufacturer of bowel preparations that compete with sodium phosphate.

First, in his conclusions regarding the risks of sodium phosphate products, Dr. DiPalma has ignored the weight of the evidence and FDA's own exhaustive review of this issue. In a series of lengthy Federal Register notices relating to an official FDA Docket (No. 78N-036L), FDA carefully analyzed the available information regarding the safety of sodium phosphate, including the published literature and FDA's own adverse event

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database. FDA's review focused closely on electrolyte changes that may occur in patients taking sodium phosphate, and considered Dr. DiPalma's study regarding the safety of sodium phosphate that he referenced in his letter. Notably, Braintree on several occasions contributed information to this Docket. After considering all of the data regarding the sodium phosphate solution, FDA concluded that:

"The agency has not received any reports that a one-time 90 mL dose has resulted in a death or a serious adverse reaction requiring medical attention."^[1]

Dr. DiPalma should have been aware of FDA's conclusion, because he has contributed to the Docket, as has Braintree on several occasions. Dr. DiPalma's letter fails to mention the results of FDA's review of the data, or even that FDA performed a review.

Note that in the professional labeling for sodium phosphate solution, the recommended total dose of sodium phosphate solution for colon cleansing is 90 mL. This indicates that FDA has determined that sodium phosphate solution is safe when used as directed for colon cleansing. Oral sodium phosphate solution has been marketed in the United States for over 100 years, and in recent years it has been used by about 1 to 2 million persons yearly as a bowel preparation prior to colonoscopy and related procedures.^[2] We estimate that more than 10 million persons have used oral sodium phosphate solution as a bowel preparation. This vast experience indicates that when sodium phosphate is used consistently with its labeling, the transient electrolyte changes that may occur do not result in medically important clinical adverse events.

Medical problems have arisen in patients taking oral sodium phosphate solution only when this OTC product was misused. For example, consumers sometimes mistakenly ingested an entire 240 mL bottle of sodium phosphate solution, instead of the 90 mL recommended dose. Consequently, the 240 mL bottle was taken off the market to prevent such misuse, but the 90 mL bottle is still marketed.

In this regard, it is notable that the case report by Campisi et al. that was cited by Dr. DiPalma in his letter indicates that sodium phosphate solution was used in a manner grossly inconsistent with the US professional labeling for this product. This misuse, which was not mentioned by Dr. DiPalma, almost certainly contributed to the problems of the surgical patient described in the case report.

InKine believes that Diacol would be far less likely to be misused than the OTC sodium phosphate solution, because InKine intends Diacol to be a prescription product that would be sold only in bottles that provide dosing for a single colon cleansing.

In his letter, Dr. DiPalma suggests that elderly patients with bone disease may be at increased risk from sodium phosphate bowel preparations. This suggestion appears to be based primarily on the Campisi report described above, regarding a single surgical patient in whom sodium phosphate solution was misused. Dr. DiPalma's suggestion is not

consistent with the available information regarding the safety of sodium phosphate, including data from the enclosed reproduction of a poster presentation. The poster was presented at the 1999 annual meeting of the American College of Gastroenterology, and describes InKine's two large, identical, investigator-blinded, controlled trials comparing

Diacol to Cherry Flavor NuLYTELY® in 845 patients undergoing colonoscopy. Notably, these trials had no exclusion criteria based on gender, advanced age, the presence of bone disease, or the use of medicines for the treatment or prevention of bone disease, as the poster indicates. While the poster states that "minor, transient" electrolyte shifts were reported in patients who took Diacol, they were "clinically insignificant," and, "In no case were clinical symptoms related to these electrolyte shifts." In addition, although we have no information on the age breakdown of the patients who have used the oral sodium phosphate solution in clinical practice over more than 100 years, it is probable that a million or more elderly patients (many with osteoporosis) have received this product as directed with no reported medically important clinical adverse events due to electrolyte changes.

The poster referenced above describes other important safety information from InKine's two large controlled trials. The poster indicates that in these studies, significantly fewer patients in the Diacol group reported the common purgative-associated adverse events of nausea, vomiting, and bloating, compared to NuLYTELY. There was no significant difference in the rate of the other common gastrointestinal symptom, abdominal pain, in the two studies combined. Sodium phosphate tablets, like sodium phosphate solution, are quite safe when used as directed.

As FDA is aware, Braintree has previously tried to disparage the safety of sodium phosphate products to the Agency and to physicians. Sadly, Dr. DiPalma's letter is consistent with this pattern of disparagement.

Thus, Dr. DiPalma's letter sheds no new light on the already settled issue of the safety of sodium phosphate, which is safe when used as directed. Sodium phosphate solution has been used for over 100 years in the US. We estimate that it has been taken by more than 10 million Americans as a bowel preparation. This vast experience indicates that when sodium phosphate is used consistently with its labeling, the transient electrolyte changes that may occur do not result in medically important clinical adverse events.

Second, we think it most regrettable that Dr. DiPalma failed to disclose in his letter his long and continuing history of close involvement with Braintree, the manufacturer of NuLYTELY and GoLYTELY®. A recent publication regarding a Braintree product by Dr DiPalma and others reveals that,

"Dr. DiPalma serves as a medical director/consultant to Braintree Laboratories ..." [3]

Dr. DiPalma's role as a medical director/consultant to Braintree raises a significant conflict of interest here because Braintree's products compete in the market with sodium phosphate bowel preparation products. Braintree would profit substantially if sodium phosphate products were no longer marketed in the US.

In addition, over the period from 1984 to 2000, Dr. DiPalma authored at least 13 published reports (including one on-line report) of investigations of the safety and efficacy of bowel preparations.^[4] With one exception, all of the reported studies involved Braintree products. The sole exception was a clinical study (funded by Braintree) that dealt with a purported safety risk of a competing product. Of the 13 publications, only five included information regarding the source of support for the study. In all five cases, Braintree provided support for the study. In the other eight publications, the sources of support for the studies were not revealed. Also, FDA documents available to the public indicate that Dr. DiPalma was an investigator in at least one multicenter NDA study for a Braintree product that was performed prior to 1989. Thus, Dr. DiPalma has performed many studies for Braintree, consistent with his role as a medical director/consultant of that corporation.

Notably, Dr. DiPalma is listed in the 2000 Physician's Desk Reference (PDR) as the emergency medical contact for Braintree.

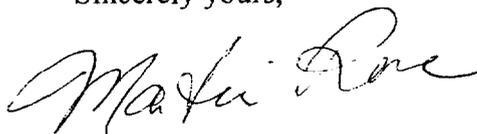
Dr. DiPalma wrote his letter to FDA on University of South Alabama stationery. His signature block included his academic title, but he never mentioned his many ties to Braintree or his role in the corporation. This gives the letter an air of academic impartiality and lack of pecuniary interest that is misleading. It was wrong for Dr. DiPalma not to reveal his relationship with Braintree. A simple statement like the one quoted above from his recent paper would have sufficed.

Three documents referenced above are enclosed and may be of interest to FDA. The first is a copy of Dr. DiPalma's recent paper in the American Journal of Gastroenterology that reveals his close ties to Braintree. The second is a copy of the first page of the 2000 PDR listing for Braintree products that indicates that he is Braintree's emergency medical contact. The third is a reproduction of the previously-cited peer-reviewed poster that was presented at the 1999 annual meeting of the American College of Gastroenterology. This poster describes the design and results of InKine's randomized, controlled, investigator-blinded studies comparing Diacol and Cherry Flavor NuLYTELY in patients undergoing colonoscopy. The authors of this poster conclude that compared to NuLYTELY, Diacol was "equivalent ... in the efficacy of colon cleansing"; "the incidence of the common gastrointestinal side effects of purgation, nausea, vomiting, and bloating were reported much less often in those patients who took Diacol"; and that Diacol was better accepted than NuLYTELY by patients in a variety of ways. The authors also conclude that Diacol use caused "minor, transient clinically insignificant electrolyte shifts, which self-corrected within 48 to 72 hours, more often than did

NuLYTELY.” The results of these studies strongly support the safety and efficacy of Diacol Tablets as a colon cleansing agent.

Thank you for your consideration.

Sincerely yours,



Martin Rose, M.D., J.D.
Senior Vice President
Clinical Research and Regulatory Affairs

cc: Lilia Talarico, M.D. (HFD-180)
Charles Ganley, M.D. (HFD-560)
Cheryl Turner (HFD-560)

^[1] 63 FR 27836, 27838 (May 21, 1998).

^[2] Kolts BE. Letter. Am J Gastroenterology 1994;89:1119. The letter includes data from 1988 to 1994 regarding sales of sodium phosphate “kits” containing 45 mL bottles of sodium phosphate solution for oral use, but not for the 45 or 90 mL bottles sold separately. Clinical use of sodium phosphate has increased significantly since 1994. InKine is continuing to gather data on the use of oral sodium phosphate solution.

^[3] DiPalma JA, DeRidder PH, Orlando RC, Kolts BE, Cleveland MvB. A randomized, placebo-controlled, multicenter study of the safety and efficacy of a new polyethylene glycol lavage. Am J Gastroenterology 2000;95:447-450. A copy of this publication is enclosed.

^[4] Twelve of these were clinical studies and one was a veterinary study.

ATTACHMENTS

- 1. Journal Article**
- 2. Copy of PDR Page**
- 3. Poster Reproduction**

A Randomized, Placebo-Controlled, Multicenter Study of the Safety and Efficacy of a New Polyethylene Glycol Laxative

Jack A. DiPalma, M.D., Peter H. DeRidder, M.D., Roy C. Orlando, M.D., Byron E. Kolts, M.D., and Mark vB. Cleveland, Ph.D.

Divisions of Gastroenterology, University of South Alabama College of Medicine, Mobile, Alabama; William Beaumont Hospital, Royal Oak, Michigan; Tulane University School of Medicine, New Orleans, Louisiana; University of Florida Health Science Center, Jacksonville, Florida; and Braintree Laboratories Inc., Braintree, Massachusetts

OBJECTIVE: This study was designed to determine the efficacy and safety of a new laxative, Braintree polyethylene glycol (PEG) laxative (Miralax, Braintree Laboratories, Braintree, MA).

METHODS: This investigation was designed as a placebo-controlled, blinded, randomized, multicenter parallel trial. Study subjects were constipated but otherwise healthy outpatients who had ≤ 2 stools during a 7-day qualification period. Braintree PEG laxative 17 g or dextrose placebo *p.o.* in 8 oz of water for a 14-day treatment period. A diary recorded each bowel movement and subjective symptoms of stool consistency, ease of passage, cramps, and flatus. CBC, blood chemistries and urinalysis were performed before and after the treatment period.

RESULTS: There were 151 randomized subjects, 131 female and 20 male. An increase in bowel movement frequency was observed with the PEG laxative as compared to placebo ($p < 0.001$), with the greatest difference in efficacy in wk 2 of treatment ($p < 0.001$). By wk 2 of treatment, on average, placebo subjects had 2.7 bowel movements/wk and PEG-treated study subjects had 4.5 movements/wk ($p < 0.01$), or more than one bowel movement every 2 days. Investigator ($p < 0.005$) and patient ($p < 0.001$) subjective assessment of perception of treatment effectiveness, and patient evaluations of stool consistency and passage showed significant improvement in the active treatment group ($p < 0.001$). There were no significant differences in laboratory changes or adverse experiences recorded between groups.

CONCLUSION: Braintree PEG laxative is safe and effective in the short term for the treatment of constipation. (Am J Gastroenterol 2000;95:446-450. © 2000 by Am. Coll. of Gastroenterology)

INTRODUCTION

Luminous liquid stool is produced by polyethylene glycol electrolyte lavage solutions (PEG-ELS) when given to

cleanse the GI tract for diagnostic or surgical procedures (1-3). It is, therefore, not surprising that clinicians have used these solutions for treating constipation (4-7). Whereas PEG-ELS ingested at a rate of 1.5 L/h reaches a steady state with no net absorption or secretion of water and electrolytes (1), the same cannot be said for low volume administration (8). Although clearly effective (4), small volume PEG-ELS can be hazardous in some patients and should be used cautiously for chronic, idiopathic constipation because of absorption of the salt component of the solution (8) (M. Reichelderfer, unpublished observations, University of Wisconsin, Madison, WI, 1999).

A new, tasteless laxative, the Braintree PEG laxative (Miralax, Braintree Laboratories, Braintree, MA) has been developed. It is composed of PEG 3350 (PEG 3350) and, unlike the lavage solutions, there is no salt absorption (8) (M. Reichelderfer, unpublished observations, University of Wisconsin, Madison, WI, 1999).

PEG 3350 is a chemically inert polymer of the formula $H(OCH_2CH_2)_nOH$ where $n = 68-84$. It has been shown to be remarkably nontoxic and can be ingested in large quantities without harmful effects (9, 10). PEG 3350 is absorbed only in trace amounts from the GI tract (10, 11). It is highly soluble and in solution it will bind or sequester water molecules (12). This osmotic effect makes PEG an excellent candidate as a new laxative to treat idiopathic constipation. This investigation was designed to determine the safety and efficacy of Braintree PEG laxative over a 2-wk treatment period.

MATERIALS AND METHODS

Study Population

Study subject candidates who reported a history of constipation were evaluated for enrollment in a 7-day qualification period, in which they were given a diary and asked to record all bowel movements. If they had more than two bowel movements during a 7-day period they were enrolled in this

placebo-controlled, blinded, randomized, multicenter parallel trial. Study subjects were excluded if they had allergy or sensitivity to PEG, prior GI surgery, known or suspected GI obstruction, ileus, heart failure, renal failure, ascites, other known chronic bowel, liver, renal or cardiopulmonary disorders, if they were pregnant or lactating, or if they weighed <100 lb. Study subjects were enrolled at four centers, all of which used the same investigation protocol. Study subjects were recruited from gastroenterology practices and by local advertising. The experimental protocol was approved by the respective institutional review boards. Written, informed consent was obtained from all subjects before initiation of the study.

Baseline Evaluation

At baseline, history and physical examination were performed recording age, sex, and weight and subjects were screened for exclusions. CBC, serum chemistries, urinalysis, and stool occult blood were performed. Barium enema and sigmoidoscopy examination or colonoscopy was performed as indicated after the study if such examinations had not been performed within the last 2 yr. Any additional evaluations were performed at the discretion of each investigator. Other than for suspected mechanical obstruction, no attempt was made to separate patients with anorectal (pelvic floor) dysfunction from colonic inertia by diagnostic methodology.

Study Medication

Enrolled subjects were randomly assigned to a treatment schedule according to a table of random numbers. During a 14-day treatment period they were instructed to take either 17 g of PEG laxative or dextrose powder placebo *p.o.* daily. Patients and investigators were unaware as to which was active drug or placebo. The dose of 17 g was selected based upon previous unpublished studies (M. Reichelderfer), which suggested 17 g as a minimally effective dose. The study drug was provided in a polyethylene jar containing 255 g of test material. Each patient was issued a plastic scoop that would deliver the appropriate dose. They were instructed to mix a single scoop in approximately 8 oz of water or juice and to drink one dose of the test material each day.

Monitoring

Patients were provided with diary sheets to record each bowel movement and associated subjective symptoms rating stool consistency, ease of passage, cramps, and flatus. Investigators and patients were asked to make a global assessment as to whether or not they felt the treatment was effective. Study subjects were allowed to withdraw from the study because of either perceived lack of efficacy or diarrhea. In practice, some patients responded to perceived lack of efficacy by giving themselves a different laxative or enema. These were scored and analyzed as treatment failures. CBC, blood chemistry, and urinalysis were performed after the 14-day treatment period.

Table 1. Comparison of Efficacy Data

	PEG Laxative	Placebo	<i>p</i>
Treatment success (wk 1 and 2)	72.2%	49.6%	<0.001
Success wk 1	68.5%	50.7	<0.04
Success wk 2	76.1%	48.4%	<0.001
Intent-to-treat success*	65.8%	47.8%	<0.005
Investigator-rated effectiveness	71.4%	47.1%	<0.005
Patient-rated effectiveness	67.6%	40.3%	<0.001

* For overall treatment and analysis of intent-to-treat success, the percentages represent the responses of both treatment weeks.
PEG = polyethylene glycol.

Data Analysis

Bowel movement frequency was analyzed by χ^2 analysis. This included both an analysis of the entire 14 day period as well as the first and second 7-day segments within the treatment period. Efficacy analysis included an "evaluable" analysis and an "intent-to-treat" analysis. In the evaluable analysis, only patients completing ≥ 1 wk of treatment were considered. In the intent-to-treat analysis, all patients entering the treatment phase were included. For all analyses, an effective treatment was defined as >3 bowel movements per 7-day period. A treatment failure was >3 bowel movements per 7-day period, use of laxatives or enemas, or withdrawal. Student's *t* test was used to compare weekly bowel movement averages between groups. Subjective criteria were tested using χ^2 with continuity correction, and laboratory data were compared by repeated measures of analysis of variance. A value $p < 0.05$ was considered statistically significant.

RESULTS

A total of 151 consenting adult subjects were randomized. There were 131 women and 20 men. In all, 13 men and 67 women were randomized to receive the PEG laxative, and seven men and 64 women the placebo (*p* not significant). There were 46 enrolled at the Mobile site, 50 at Royal Oak, 32 at New Orleans, and 23 at Jacksonville. The average age of study subjects was 45.2 yr. Subjects randomized to PEG were 46.7 yr \pm 14 SD and placebo 45.8 yr \pm 13.3 S.D. Therefore, efficacy analysis was based on 144 patients. Seven were excluded because of noncompliance or prestudy laboratory abnormality. A total of 135 completed the protocol. Data from all enrolled study subjects were included in safety-related analysis and laboratory data analysis.

The four study centers were similar in their proportion of male to female patients and mean ages. The patients in each of the study centers were also similar in their response to treatment, therefore, the data from all centers were combined and analyzed as a single study for presentation.

There was a highly statistically significant response to PEG laxative as compared to placebo considering both wk 1 and 2 of treatment together, separately or on an intent-to-treat basis (Table 1). On average, by wk 2 of treatment, PEG resulted in 4.5 bowel movements weekly, whereas placebo

Table 2. Number of Bowel Movements

	PEG Laxative*	Placebo	p
Wk 1†	4.2 ± 2.8	2.9 ± 1.9	<0.01
Wk 2	4.5 ± 3.0	2.7 ± 1.8	<0.001

* Data are given as mean ± SD.

† Data are from individuals who completed ≥3 days of treatment and who did not report diarrhea.

PEG = polyethylene glycol.

resulted in 2.7 movements weekly (Table 2). Investigator and patient overall rating of effectiveness showed that there was a perception of significantly better efficacy associated with the laxative. Patient ratings of subjective observations associated with each bowel movement during treatment are shown in Table 3. During the pretreatment qualification period, there were no differences seen between groups for those patients that reported their stool consistency as hard with difficult passage, or symptoms of severe cramping or gas. During the treatment period, significantly fewer patients in the PEG laxative group reported hard stool consistency or difficult passage as compared to placebo. The percentage of bowel movements rated as "satisfactory" was consistent with the treatment efficacy data where 68% of bowel movements during PEG treatment were rated as satisfactory versus 46% during placebo treatment. During the treatment period, PEG laxative subjects also reported significantly less cramping and gas (Table 3). No statistically or clinically significant differences between placebo and laxative groups were detected for laboratory measurements. There were also no differences between treatment groups for adverse events.

DISCUSSION

Patients reporting constipation may be describing stools that are too small, too hard, or too infrequent (13). The strict definition used in this study was fewer than three stools weekly. Although various definitions make epidemiological reporting difficult, it has been estimated that constipation affects one in 50 Americans (14) and accounts for as many as 2.5 million office visits a year, corresponding to a 1.2% prevalence (15). Female gender, African-American race, low physical activity, fewer years of education, and symp-

oms of depression are independent risk factors for impaired bowel function (16, 17). The consequences of this disorder include fecal impaction with incontinence or obstruction and perforation. Mortality among patients with impaction and perforation has been reported to range from 0 to 16% (18). In the elderly or institutionalized, presenting signs may be misleading and acute confusional states are common. Healthy, ambulatory patients may have intractability requiring surgical therapy (19). Thus, constipation deserves attention as a condition of clinical, social, and economic importance.

The medical treatment of constipation is as varied and subjective as its definition. A reasonable approach incorporates a thorough medical history and physical examination to detect associated metabolic, endocrine, and neurogenic conditions, and medications (20). A diagnostic evaluation should include a structural examination of the colon. Patients should be educated about good defecatory and eating habits. High fiber diet and avoidance of "stimulant" laxatives are tenets of therapy; however, further treatment guidelines are poorly organized (20). Most practitioners begin with bulk agents and add hyperosmolar, saline, lubricant, emollient, or stimulant laxatives as necessary (20-23). These measures are often inadequate, and patients may not have satisfactory results despite additional medications and combination regimens.

The results of this study are similar to previous studies which have successfully used small daily doses of PEG electrolyte solutions (PEG-ELS, GoLytely) for treating constipation (4, 5). The primary osmotically active component of these solutions is PEG 3350 (PEG-3350) which acts to retain water in the gut (12). In the present study, laxation was effected using only PEG 3350 without the extraneous salts contained in the PEG-electrolyte lavage products. When used in small doses the salts in the PEG-ELS solutions have been shown to be absorbed (8) (Reichelderfer, in preparation), which could significantly add to patient sodium load. The 500-ml does of PEG-electrolyte solution found effective by Andorsky *et al.* would provide a daily sodium load of nearly 3 g (4). Polyethylene glycol 3350 is not metabolized by bowel flora and is not significantly absorbed (11, 24). Therefore, this inert polymer is an excellent candidate as a new osmotic laxative without the

Table 3. Patient Ratings of Subjective Observations

	PEG Laxative	Placebo	p
Hard stool consistency, difficult Passage			
Pretreatment qualification period	75.2%	75.5%	0.64
Treatment period	13.8%	46.4%	0.001
Severe cramping			
Pretreatment qualification period	35.5%	39.2%	0.61
Treatment period	12.0%	22.6%	0.001
Severe gas			
Pretreatment qualification period	49.5%	60.7%	0.13
Treatment period	24%	40.2%	0.001

PEG = polyethylene glycol.

problems associated with other osmotic laxatives. The most recently FDA approved laxative, lactulose (which was approved in 1979) is a poorly absorbed synthetic disaccharide. It is metabolized by bowel flora to organic acids resulting in water retention in the intestinal lumen (8). The metabolic activity associated with lactulose administration can result in gas with attendant abdominal discomfort, and eventual adaptation of bowel flora all of which tend to reduce effectiveness (8, 25). PEG-3350 laxative reduced complaints of gas nearly in half over placebo. The saline laxatives, magnesium, and sodium phosphate salts, are associated with significant absorption of their component ions, which can result in systemic toxicity including dehydration, magnesium intoxication, and electrolyte abnormalities including potassium and calcium depletion (26). This presents an acute problem for renal and heart patients; therefore, labeling for these products cautions against use in such patients. As shown in this study, the PEG 3350 laxative does not affect patient electrolytes or serum osmolality.

This study confirms the safety and efficacy of Braitree PEG laxative (Miralax) for the short term treatment of constipation, but long term safety and efficacy was not evaluated in this study. Bowel movement frequency was increased in the active treatment group compared to placebo and patient evaluation of stool passage and consistency was favorable in the PEG laxative group. Investigators and patients rated subjective assessment of treatment effectiveness superior in the treatment group. There were no adverse experiences or clinically significant laboratory abnormalities.

In conclusion, Braitree PEG laxative is effective for increasing bowel movement frequency, and improving stool consistency and ease of passage in ambulatory patients meeting a strict definition of constipation. It was well tolerated by study subjects and will likely find a role in the therapeutic armamentarium for constipation.

ACKNOWLEDGMENTS

This work was supported by a grant from Braitree Laboratories, Braitree, MA. Dr. DiPalma serves as a medical director/consultant to Braitree Laboratories and Dr. Cleveland is Senior Vice President, New Drug Development, Braitree Laboratories. Statistical analysis performed by Wayne P. Pierson, Ph.D. The authors express their appreciation to research assistants Emilie D. Barnett, R.N., Jennifer F. Chastang, R.N., William Chiapetta, Vivian Caballero, and Sally Thayer, to Dr. Geoffrey Clark for literature review, and to Tonya J. Beacham for administrative support.

Reprint requests and correspondence: Jack A. DiPalma, M.D., Director, Division of Gastroenterology, University of South Alabama, 3301 Knollwood Drive, Building D, Mobile, AL 36693.

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Serentil—Cont.

tients a starting dose of 25 mg is recommended. The dose may be repeated in 30 to 80 minutes, if necessary. The usual optimum total daily dose range is 26-200 mg per day.

HOW SUPPLIED

Tablets: 10 mg (NDC 0597-0020-01), 25 mg (NDC 0597-0021-01), 50 mg (NDC 0597-0022-01), and 100 mg (NDC 0597-0023-01) mesoridazine (as the besylate). Bottles of 100. Ampuls: 1 mL (25 mg mesoridazine (as the besylate)). Boxes of 20 (NDC 0597-0027-02).

Concentrate Contains 25 mg mesoridazine (as the besylate) per mL, alcohol, USP, 0.61% by volume. Immediate containers: Amber glass bottles of 4 fl oz (118 mL) packaged in cartons of 12 bottles, with an accompanying dropper graduated to deliver 10 mg, 25 mg, and 50 mg of mesoridazine (as the besylate) (NDC 0597-0025-04).

STORAGE

Tablets: Below 86°F (30°C). Injection: Below 86°F (30°C); protect from light. Oral solution: Below 77°F (25°C); protect from light; dispense in amber glass bottles only.

The concentrate may be diluted with distilled water, acidified tap water, orange juice or grape juice. Each dose should be diluted just prior to administration. Preparation and storage of bulk dilutions is not recommended.

Additional information available to physicians.

PHARMACOLOGY

Pharmacological studies in laboratory animals have established that Serentil® (mesoridazine besylate) has a spectrum of pharmacodynamic actions typical of a major tranquilizer. In common with other tranquilizers it inhibits spontaneous motor activity in mice, prolongs thiopental and hexobarbital sleeping time in mice and produces aphasia and block of arousal reaction in the EEG of rabbits. It is effective in blocking spinal reflexes in the cat and antagonizes d-amphetamine excitation and toxicity in grouped mice. It shows a moderate adrenergic blocking activity in vivo and in vivo and antagonizes 5-hydroxytryptamine in vivo. Intravenously administered, it lowers the blood pressure of anesthetized dogs. It has a weak anticholinergic effect in vitro.

The most outstanding activity of Serentil® (mesoridazine besylate) is seen in tests developed to investigate antiemetic activity of drugs. Such tests are those in which the rat reacts to acute or chronic stress by increased defecation (emotogenic defecation) or tests in which "emotional mydriasis" is elicited in the mouse by an electric shock. In both of these tests Serentil® (mesoridazine besylate) is effective in reducing emotive reactions. Its ED₅₀ in inhibiting emotogenic defecation in the rat is 0.053 mg/kg (subcutaneous administration). Serentil® (mesoridazine besylate) has a potent antiemetic action. The intravenous ED₅₀ against apomorphine-induced emesis in the dog is 0.64 mg/kg. Serentil® (mesoridazine besylate), in common with other phenothiazines, demonstrates antirhythmic activity in anesthetized dogs.

Metabolic studies in the dog and rabbit with tritium labeled mesoridazine demonstrate that the compound is well absorbed from the gastrointestinal tract. The biological half-life of Serentil® (mesoridazine besylate) in these studies appears to be somewhere between 24 and 48 hours. Although significant urinary excretion was observed following the administration of Serentil® (mesoridazine besylate), these studies also suggest that biliary excretion is an important excretion route for mesoridazine and/or its metabolites.

Toxicity Studies

Acute LD₅₀ (mg/kg):

Route	Mouse	Rat	Rabbit	Dog
Oral	560-625	644-748	MLD=900	MLD=800
I.M.	--	509M 534 F	406	--
I.V.	26-0.08	--	--	--

Chronic toxicity studies were conducted in rats and dogs. Rats were administered Serentil® (mesoridazine besylate) orally seven days per week for a period of seventeen months in doses up to 160 mg/kg per day. Dogs were administered Serentil® (mesoridazine besylate) orally seven days per week for a period of thirteen months. The daily dosage of the drug was increased during the period of this test such that the "top-dose" group received a daily dose of 120 mg/kg of mesoridazine for the last month of the study. Unfavorable effects that occurred upon chronic administration of high dose levels included:

Rats: Reduction of food intake, slowed weight gain, morphological changes in pituitary-supported endocrine organs, and melanin-like pigment deposition in renal tissues.

Dogs: Emesis, muscle tremors, decreased food intake and death associated with aspiration of oral-gastric contents into the respiratory system.

Increased intrasutaneous receptors were seen with Serentil® (mesoridazine besylate) in rats at 70 mg/kg and in rabbits

(local irritation from the intramuscular injection of Serentil® (mesoridazine besylate) was of the same order of magnitude as with other phenothiazines).

SE-PI-706 Rev

Manufactured by:
Sandoz Pharmaceuticals Corporation,
East Hanover, NJ 07938
Distributed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877

Shown in Product Identification Guide, page 308

Braintree Laboratories, Inc.

P.O. BOX 850929
BRAintree, MA 02185-0929

Direct Inquiries to:
Harry P. Keegan, President
(781) 843-2202

For Medical Information Contact:
In Emergencies:
Jack DiPalma, M.D.
(800) 874-6756

GoLYTELY®

(Go-Itz Itz)
(PEG-3350 and Electrolytes For Oral Solution)

NuLYTELY®

(New-Itz Itz)
(PEG-3350, Sodium Chloride, Sodium Bicarbonate and Potassium Chloride for Oral Solution)

DESCRIPTION

GoLYTELY®

A white powder in a 4 liter jug for reconstitution, containing 236 g polyethylene glycol 3350, 22.74 g sodium sulfate (anhydrous), 6.74 g sodium bicarbonate, 6.86 g sodium chloride, 2.97 g potassium chloride. When dissolved in water to a volume of 4 liters, GoLYTELY (PEG-3350 and electrolytes for oral solution) is an isotonic solution having a mildly salty taste. GoLYTELY is administered orally or via nasogastric tube as a gastrointestinal lavage.

NuLYTELY®

A white powder for reconstitution containing 420 g polyethylene glycol 3350, 6.72 g sodium bicarbonate, 11.2 g sodium chloride, 1.48 g potassium chloride. When dissolved in water to a volume of 4 liters, NuLYTELY (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution) is an isotonic solution having a pleasant mineral water taste. NuLYTELY is administered orally or via nasogastric tube as a gastrointestinal lavage.

CLINICAL PHARMACOLOGY

GoLYTELY and NuLYTELY induce a diarrhea which rapidly cleanses the bowel, usually within four hours. The osmotic activity of polyethylene glycol 3350 and the electrolyte concentration result in virtually no net absorption or excretion of ions or water. Accordingly, large volumes may be administered without significant changes in fluid or electrolyte balance.

INDICATIONS AND USAGE

GoLYTELY®

GoLYTELY is indicated for bowel cleansing prior to colonoscopy and barium enema X-ray examination.

NuLYTELY®

NuLYTELY is indicated for bowel cleansing prior to colonoscopy.

CONTRAINDICATIONS

GoLYTELY and NuLYTELY are contraindicated in patients known to be hypersensitive to any of the components. GoLYTELY and NuLYTELY are contraindicated in patients with gastrointestinal obstruction, gastric retention, bowel perforation, toxic colitis, toxic megacolon or ileus.

WARNINGS

GoLYTELY®

No additional ingredients, e.g. flavorings, should be added to the solution. GoLYTELY should be used with caution in patients with severe ulcerative colitis.

NuLYTELY®

No additional ingredients, e.g. flavorings, should be added to the solution. NuLYTELY should be used with caution in patients with severe ulcerative colitis. Use of NuLYTELY in children younger than 2 years of age should be carefully monitored for occurrence of possible hypoglycemia, as this solution has no caloric substrate. Dehydration has been reported in 1 child and hypokalemia has been reported in 3 children.

PRECAUTIONS

General: Patients with impaired gag reflex, unconscious, or semiconscious patients, and patients prone to regurgitation or aspiration should be observed during the administration of GoLYTELY or NuLYTELY, especially if it is administered via nasogastric tube. If a patient experiences severe bloating, distention or abdominal pain, administration should be stopped or temporarily discontinued until the

to rule out these conditions before administration of GoLYTELY or NuLYTELY.

Information for Patients: GoLYTELY and NuLYTELY produce a watery stool which cleanses the bowel before examination. Prepare the solution according to the instructions on the bottle. It is more palatable if chilled. For best results, no solid food should be consumed during the 2 to 4 hour period before drinking the solution, but in no case should solid foods be eaten within 2 hours of taking GoLYTELY or NuLYTELY.

GoLYTELY®: Drink 240 mL (8 oz.) every 10 minutes. Rapid drinking of each portion is better than drinking small amounts continuously.

NuLYTELY®: Adults drink 240 mL (8 oz.) every 10 minutes. Pediatric patients (aged 6 months or greater) drink 25 mL/kg/hour. Use of NuLYTELY in children younger than 2 years of age should be carefully monitored for occurrence of possible hypoglycemia, as this solution has no caloric substrate. Dehydration has been reported in 1 child and hypokalemia has been reported in 3 children.

The first bowel movement should occur approximately one hour after the start of GoLYTELY or NuLYTELY administration. You may experience some abdominal bloating and distention before the bowel starts to move. If severe discomfort or distention occur, stop drinking temporarily or drink each portion at longer intervals until these symptoms disappear. Continue drinking until the watery stool is clear and free of solid matter. This usually requires at least 3 liters and it is best to drink all of the solution. Any unused portion should be discarded.

Drug Interactions: Oral medication administered within one hour of the start of administration of GoLYTELY or NuLYTELY may be flushed from the gastrointestinal tract and not absorbed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenic and reproductive studies with animals have not been performed.

Pregnancy: Category C. Animal reproduction studies have not been conducted with GoLYTELY and NuLYTELY. It is also not known whether GoLYTELY and NuLYTELY can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. GoLYTELY and NuLYTELY should be given to a pregnant woman only if clearly needed.

Pediatric Use:

GoLYTELY®

Safety and effectiveness in children have not been established.

NuLYTELY®

Safety and effectiveness of NuLYTELY in pediatric patients aged 6 months and older is supported by evidence from adequate and well-controlled clinical trials of NuLYTELY in adults with additional safety and efficacy data from published studies of similar formulations.

ADVERSE REACTIONS

Nausea, abdominal fullness and bloating are the most common adverse reactions (occurring in up to 50% of patients) to administration of GoLYTELY or NuLYTELY. Abdominal cramps, vomiting and anal irritation occur less frequently. These adverse reactions are transient and subside rapidly. Isolated cases of urticaria, rhinorrhea, dermatitis and (rarely) anaphylactic reaction have been reported which may represent allergic reactions.

DOSAGE AND ADMINISTRATION

GoLYTELY®

The recommended dose for adults is 4 liters of GoLYTELY solution prior to gastrointestinal examination, as ingestion of this dose produces a satisfactory preparation in over 96% of patients. Ideally, the patient should fast for approximately three or four hours prior to GoLYTELY administration, but in no case should solid food be given for at least two hours before the solution is given.

GoLYTELY is usually administered orally, but may be given via nasogastric tube to patients who are unwilling or unable to drink the solution. Oral administration is at a rate of 240 mL (8 oz.) every 10 minutes, until 4 liters are consumed or the rectal effluent is clear. Rapid drinking of each portion is preferred to drinking small amounts continuously. Nasogastric tube administration is at the rate of 20-30 mL per minute (1.2-1.8 liters per hour). The first bowel movement should occur approximately one hour after the start of GoLYTELY administration.

Various regimens have been used. One method is to schedule patients for examination in midmorning or later, allowing the patient three hours for drinking and an additional one hour period for complete bowel evacuation. Another method is to administer GoLYTELY on the evening before the examination, particularly if the patient is to have a barium enema.

NuLYTELY®

NuLYTELY is usually administered orally, but may be given via nasogastric tube to patients who are unwilling or unable to drink the solution. Ideally, the patient should fast for approximately three or four hours prior to NuLYTELY administration, but in no case should solid food be given for at least two hours before the solution is given.

Oral administration:

Adults: At a rate of 240 mL (8 oz.) every 10 minutes, until the rectal effluent is clear or 4 liters are consumed.

Pediatric Patients: aged 6 months or greater:

SODIUM PHOSPHATE TABLETS (INKP-100, DIACOL™) ARE SAFE AND EFFECTIVE AS A PURGATIVE FOR COLONOSCOPY.

D. Kastenber MD, C. Choudhary MD, E. Weiss MD, S. Steinberg MD FACG, and the INKP-100 Study Group. Thomas Jefferson University, Philadelphia PA; Cleveland Clinic Florida, Fort Lauderdale FL; Univ. of Colorado, Denver CO.

BACKGROUND: The preparations GoLYTELY, CoLYTE, NuLYTELY, and Fleets Phospho-Soda, all currently used for colonoscopy preparation, present a serious barrier to the wider use of this important screening tool. The copious volume and unpleasant taste of the PEG solutions, and the unpleasant taste of Fleets Phospho-Soda, has led to the development of an oral tablet formulation of sodium phosphate salts in an attempt to provide a safe, effective and acceptable oral purgative preparation.

OBJECTIVE: To compare the safety, efficacy and patient acceptance of a tablet formulation of sodium phosphate salts with the most frequently prescribed PEG purgative, Cherry Flavor NuLYTELY.

METHODS: Two large, randomized, parallel-group, multicenter, investigator-blinded clinical trials were conducted in 845 patients scheduled for colonoscopy.

Exclusion criteria:

1. Renal: creatinine >2.0 mg/L preexisting electrolyte abnormality
2. Cardiovascular: uncontrolled congestive heart failure acute MI within 3 months CABG within 3 months angioplasty within 3 months
3. Gastrointestinal: Ascites inability to swallow tablets Symptomatic IBD Chronic constipation (2 BM's/week or less) Hypomotility syndromes - megacolon, pseudoobstruction Colectomy: >50% of colon
4. Any condition that the investigator thought might interfere with assessment of efficacy or present an increased safety risk to the patient

After signing informed consent, and qualifying by baseline assessments, the patient was randomized to take either Diacol tablets or Cherry Flavor NuLYTELY as the purgative for colonoscopy.

STUDY PRODUCT DOSING:

Diacol tablets: Day prior to colonoscopy

1. Clear liquids after normal breakfast
2. 6 PM: 3 tablets with 8 ounces clear liquids of choice q 15 minutes for a total of 20 tablets

Day of Colonoscopy

1. 3 to 5 hours before colonoscopy, repeat dosing as above

NuLYTELY liquid:

Day prior to colonoscopy, according to the product information sheet

1. Clear liquids after normal breakfast
2. One 8 ounce glass NuLYTELY every 10 minutes for 16 glasses to complete four liters

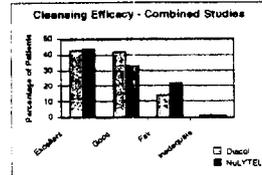
STUDY PROCEDURES:

VISIT	HAEM	BAG	TELE	NO. OF TABLETS TAKEN	ADVERSE EVENTS	COLONOSCOPY COMPLETED	INTERVIEWER QUANTITATIVE CLEANSING ASSESSMENT
Baseline	X	X	X	X			
VISIT 1 (48-72 hrs)	X	X	X	X	X	X	X
VISIT 2 (48-72 hrs)	X	X	X	X			

STATISTICAL METHODS:

This study was powered for equivalence, not for superiority of one product over another. At the time of colonoscopy, the physician used a validated 4-point scale ranging from "1-excellent" to "4-inadequate-repreparation required" to indicate the degree of colon cleansing. (SEE POSTER # 493) The primary efficacy parameter, the equivalence in quality of colonic purgation between the 2 study products was assessed using 2 one-sided t-tests. Each t-test had the hypothesis that there was no more than a 0.3-point difference in the mean scores between the 2 study products. The distribution of scores by site and study product group was also assessed.

RESULTS: 1. EFFICACY: By means of a validated Physician Questionnaire, gastroenterologists who were blinded to the prep used, assessed the quality of colon cleansing. Diacol tablets were equivalent in efficacy to NuLYTELY for all categories of patients. Fewer than 2% of patients in each product group revealed which product they took to their physician.



	DIACOL	NuLYTELY
1-Excellent	179 (42.6%)	183 (43.2%)
2-Good	173 (41.7%)	141 (33.2%)
3-Fair	60 (14.2%)	54 (12.2%)
4-Inadequate, reprep	6 (1.4%)	3 (1.2%)
Total number	422	423

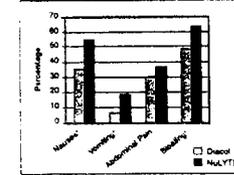
There was no difference in the distribution of cleansing results between the two study groups in either study. Note that in Study #2, there was a trend toward statistically greater efficacy in cleansing for Diacol tablets (p<0.064).

Overall Quality of Cleansing

STUDY #1	STUDY #2	COMBINED STUDIES	
		DIACOL	NuLYTELY
Quant	Qual	Quant	Qual
Mean	Mean	Mean	Mean
1.881	1.838	1.887	1.883
1.946	1.910	1.946	1.899
95% CI	95% CI	95% CI	95% CI
0.758	0.237	0.146	0.05-0.38
0.04-0.17			
p value		0.4311	0.0647
			0.1175

*p value from a 2-sided t-test halved to make a one-sided p-value
† not significantly different
Mean score determined from physician assessment: "excellent"=1, "good"=2, etc. lower score=better cleansing

2. SAFETY: The only commonly experienced adverse events were gastrointestinal symptoms associated with the purgative. All other side effects occurred in 3% or fewer patients. Nausea, vomiting and bloating were significantly less common in patients who took Diacol tablets. In one study, abdominal pain was significantly less common in Diacol patients.



PERCENTAGE OF PATIENTS REPORTING EXPECTED GI SYMPTOMS COMBINED STUDIES

	DIACOL	NuLYTELY	p value
NAUSEA	35.6	34.3	<0.0001
VOMITING	6.3	18.5	<0.0001
ABDOMINAL PAIN	30.2	36.9	<0.0001
BLOATING	48	63.7	<0.0001

Minor transient aberrations of serum electrolyte values occurred more often in patients taking Diacol. In no case were clinical symptoms related to these electrolyte shifts.

MEAN CHANGES (± S.D.) FROM BASELINE IN ELECTROLYTE VALUES

	DIACOL		NuLYTELY	
	VISIT 1 (48 to 72 hours later)	VISIT 2 (48 to 72 hours later)	VISIT 1 (48 to 72 hours later)	VISIT 2 (48 to 72 hours later)
Ca ⁺⁺	-0.5 ± 0.5	-0.1 ± 0.4	-0.1 ± 0.4	-0.1 ± 0.4
PO ₄ ⁻³	3.7 ± 1.5	-0.7 ± 0.6	0.0 ± 0.5	0.0 ± 0.6
Na ⁺	2.3 ± 2.7	0.3 ± 2.2	0.7 ± 2.4	0.0 ± 2.3
K ⁺	-0.6 ± 0.4	-0.1 ± 0.4	-0.1 ± 0.4	-0.1 ± 0.4

Two episodes of atrial fibrillation occurred in the combined trials, one in each treatment group, each without significant electrolyte shifts. The patient who took Diacol had no prior history of cardiac disease; he sensed his irregular heart rhythm and received treatment. The patient who took NuLYTELY had a heart disease and intermittent AF; he received no treatment and the arrhythmia spontaneously resolved. Both patients had significant vomiting before the arrhythmias.

3. PATIENT PREFERENCE: The following responses were obtained from patients immediately after they completed their oral cleansing preparation:

	DIACOL	NuLYTELY	p value
Completed the prep?	94%	57.2%	<0.0001
Moderately or extremely difficult to take?	11.6%	39.5%	<0.0001
Barely Tolerable or Intolerable Taste?	1.0%	23.5%	<0.0001
Would take the same preparation if future?	90.7%	67.1%	<0.0001
Prefer tablets over liquid prep for colonoscopy?	50.2%	16.2%	<0.0001
Took tablets			<0.0001
Took liquid			<0.0001

CONCLUSIONS:

1. Sodium Phosphate tablets (Diacol) are equivalent to NuLYTELY in the efficacy of colonic cleansing when used to prepare a patient for colonoscopy.
2. The incidence of common gastrointestinal side effects of purgation, nausea, vomiting, and bloating were reported much less often in those patients who took Diacol; all other clinical side effects occurred at the same rate.
3. Diacol tablets caused minor, transient clinically insignificant electrolyte shifts, which self-corrected within 48 to 72 hours, more often than did NuLYTELY.
4. Patients who took Diacol tablets found it easier to complete their prescribed dose, compared to those who took NuLYTELY.
5. Patients who took Diacol tablets tolerated the taste much better, compared to those who took NuLYTELY.
6. Patients who took Diacol were much more likely to accept the same drug for a future colonoscopy.
7. Patients who took either drug in this study preferred to take tablets for a future colonoscopy.

DIACOL tablets have been demonstrated to be equally effective in colon cleansing, to be safe, to be associated with a much lower incidence of expected gastrointestinal side effects, and to be much preferred by patients needing colonoscopy. Future studies will explore whether these easier-to-tolerate DIACOL purgative tablets will lead to better patient compliance with recommended colonoscopy screening or procedures.