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August 30, 1994

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
Department of Health and Human Services  
Room 1-23  
12420 Parklawn Drive  
Rockville, MD 20857

91 OCT - 9 AM 10:50

Re: Docket No. 78N-036L; 58 Fed. Reg. 46589 (Sept. 2, 1993), Laxative  
Drug Products for Over-the-Counter Human Use; Proposed Amendment  
to the Tentative Final Monograph

Ladies and Gentlemen:

Submitted herewith in triplicate are new data in response to the notice of proposed rulemaking published in the Federal Register (58:46589-96) on September 2, 1993, pertaining to the classification of docusate sodium, calcium and potassium as Category I stool softener laxative ingredients. The undersigned requests that the monograph be amended to include the combination of the stimulant laxative, bisacodyl, with docusate sodium. Portions of this document are proprietary to CIBA Consumer Pharmaceuticals and Ciba-Geigy Corporation and are clearly marked "CONFIDENTIAL". We respectfully request these documents NOT be made available for public access.

ACTION REQUESTED

CIBA Consumer Pharmaceuticals requests that the Commissioner issue an amendment to the monograph's section detailing the permitted combinations of stimulant and stool softener laxative active ingredients, 21 CFR Part 334.30 (i) to include the stimulant laxative, bisacodyl. The amendment would change the monograph wording as follows:

"Part 334- LAXATIVE DRUG PRODUCTS FOR THE OVER-THE-COUNTER HUMAN USE"

"Section 334.30 Permitted combination of active laxative ingredients.

78N-036L

C161

"Subsection 334.30 (i) The following stool softener laxative ingredient may be combined with the following stimulant laxative ingredients provided the combination is labeled according to §§ 334.60 and 334.62:

- (4) Docusate sodium identified in § 334.20(c) and bisacodyl identified in § 334.18(b)."

In support for the combination of docusate sodium and bisacodyl, we include in this submission data that were originally filed to FDA in 1969 as part of an IND for the combination. As you will find, animal toxicology studies and human clinical trials have been performed on this combination to adequately document its safety and effectiveness. Moreover, each of the two component active ingredients (docusate sodium and bisacodyl) are already generally recognized as being safe and effective for OTC use in the OTC laxative tentative final monograph.

#### Introduction

On September 2, 1993 the FDA published a notice of proposed rulemaking to amend the Tentative Final Monograph (TFM) for over-the-counter (OTC) laxative drug products. This proposed amendment includes conditions under which docusate salts are generally recognized as safe and effective and are not misbranded (Category I) as stool softeners. The FDA is allowing docusate salts to be formulated alone or in combination with certain stimulant, bulk forming and hyperosmotic laxatives in oral dosage forms. The ingredient bisacodyl was not included in the list of allowable stimulant laxative combinations (listed were casanthranol, phenolphthalein and sennosides A and B).

CIBA Consumer Pharmaceuticals is proposing that the combination of docusate sodium and bisacodyl be permitted for three reasons. First, each ingredient is Category I (safe and effective) in the Tentative Final Monograph. Second, the proposed bisacodyl and docusate sodium combination meets the criteria for Category I combinations as set forth in the 1975 Proposal to Establish Monographs for OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Products (40 FR:No. 56, March 21, 1975, 12921). Third, the additional attached data support the combination.

This combination will be labeled in accordance with 21 CFR § 334.50, 334.60 and 334.62.

### Basis for Combination Therapy

The primary diphenylmethane cathartics are phenolphthalein and bisacodyl. These agents have similar pharmacological characteristics and clinical uses<sup>1</sup>. Phenolphthalein's chemical structure is also similar to that of bisacodyl<sup>2</sup>. Therefore, one would not expect a difference in the pharmacology, toxicology, stability or compatibility of the combination of bisacodyl and docusate sodium from the already-allowable combination of phenolphthalein and docusate.

The fact that there are already a number of products on the market that contain the combination of phenolphthalein and docusate sodium also provides evidence that the proposed combination is safe and effective, and provides a benefit to consumers. Among these products are Correctol<sup>®</sup>, Extra Gentle Ex-Lax <sup>®</sup> and Feen-A-Mint<sup>®</sup>.

It is noteworthy that Boehringer Ingelheim, the previous owner/manufacturer of Dulcolax<sup>®</sup>, manufactured and marketed a combination product that contained docusate sodium and bisacodyl in Canada. This product was marketed from 1985-1986 but was discontinued due to poor sales performance.

Preclinical toxicology and clinical data are available for the proposed combination and were previously submitted to FDA via an IND for this combination. Attached are summaries as well as full reports for these studies found in Sections III and IV. Please note that the term "DOSS" appears in several of the documents. This term is an abbreviation used for the docusate sodium portion of the combination product. Overall, the data demonstrate that the combination provides a safe added benefit over administration of bisacodyl alone. Moreover, this combination of ingredients provides a rational therapeutic benefit for people suffering from hard stools, a frequent condition associated with constipation.

Limited stability data are also available for the combination of bisacodyl and docusate sodium which demonstrate the compatibility of the two active ingredient components. A tablet dosage form of product was packaged in amber glass bottles with screw caps for 12 months at 6°, 25° and 40° Celsius. Data show that after 12 months storage at 6° and 25° Celsius, the tablets met all specifications. Tablets held at 40° Celsius at 3 months were found to be within specification. The tablets did appear to slightly change color. After 3 months, the tablets held at 40° Celsius did tend to harden or "set-up" resulting in tablets which did not pass the disintegration test. These data are included herein as Section V.

In addition, an extensive literature database search was performed to obtain any available information pertaining to the safety and effectiveness of the bisacodyl and docusate sodium combination. The following sources were queried: Medline, Embase and Biosis from 1966 to present. No literature citations were found.

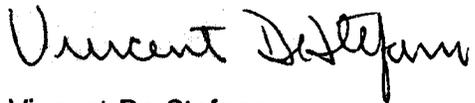
Conclusion

Since the combination of bisacodyl and docusate salts meet the three criteria outlined in the second paragraph of the INTRODUCTION section, Category I status in the OTC laxative monograph should be granted.

If there are any questions pertaining to this submission, please contact the undersigned at (908) 602-6706 or via facsimile at (908) 602-6612.

Sincerely,

CIBA Consumer Pharmaceuticals  
Division of Ciba-Geigy Corporation

A handwritten signature in cursive script that reads "Vincent De Stefano".

Vincent De Stefano  
Manager, Regulatory Affairs

CIBA Consumer Pharmaceuticals  
New Data Submission to FDA Docket 78N-036L  
August 30, 1994

### Bibliography

- 1) Goodman and Gilman; The Pharmacological Basis of Therapeutics, 6th Edition:1006, 1980.
- 2) Goodman and Gilman; The Pharmacological Basis of Therapeutics, 6th Edition:1007, 1980.

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## EXECUTIVE SUMMARY

On September 2, 1993 the FDA published a notice of proposed rulemaking to amend the Tentative Final Monograph (TFM) for over-the-counter (OTC) laxative drug products. This proposed amendment includes conditions under which docusate salts are generally recognized as safe and effective and are not misbranded (Category I) as stool softeners. The FDA is allowing docusate salts to be formulated alone or in combination with certain stimulant, bulk forming and hyperosmotic laxatives in oral dosage forms. The ingredient bisacodyl was not included in the list of allowable stimulant laxative combinations (listed were casanthranol, phenolphthalein and sennosides A and B).

CIBA Consumer Pharmaceuticals is proposing that the combination of docusate sodium and bisacodyl be permitted for three reasons. First, each ingredient is Category I (safe and effective) in the Tentative Final Monograph. Second, the proposed bisacodyl and docusate sodium combination meets the criteria for Category I combinations as set forth in the 1975 Proposal to Establish Monographs for OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Products (40 FR:No. 56, March 21, 1975, 12921). Third, the additional attached data support the combination.

This combination will be labeled in accordance with 21 CFR § 334.50, 334.60 and 334.62.

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## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

RECEIVED  
DOCKETS MANAGEMENT  
BRANCH

Public Health Service

Food and Drug Administration  
Rockville MD 20857

August 3, 1995

JUG 9

Vincent De Stefano  
Manager, Regulatory Affairs  
Ciba Self-Medication, Inc.  
Mack Woodbridge II  
581 Main Street  
Woodbridge, New Jersey 07095

Re: Docket No. 78N-036L  
Comment No. C161

Dear Mr. De Stefano:

This letter concerns your August 30, 1994 request that the tentative final monograph for over-the-counter (OTC) laxative drug products be amended to include the combination of bisacodyl and docusate sodium (DSS). This request was made in response to the notice of proposed rulemaking published in the FEDERAL REGISTER of September 2, 1993 (58 FR 46589). Your August 30, 1994 request was filed as Comment No. C161 under Docket No. 78N-036L in FDA's Dockets Management Branch on July 5, 1995.

You requested monograph status for the combination of bisacodyl and DSS for the following reasons: (1) Each ingredient was proposed as Category I (safe and effective) in the tentative final monograph; (2) the proposed bisacodyl/DSS combination meets the criteria for Category I combinations set forth in the advance notice of proposed rulemaking for OTC laxative drug products (40 FR 12921); and (3) the additional data provided support the combination. In addition, you mentioned that phenolphthalein has a chemical structure that is similar to bisacodyl. Therefore, one would not expect a difference in the pharmacology, toxicology, stability, or compatibility of the combination of bisacodyl and DSS from the already allowable combination of phenolphthalein and DSS.

You included animal toxicology studies and human clinical trial data that were originally submitted to FDA in 1969 as part of an investigational new drug application (IND) in support of the combination of bisacodyl and DSS. The safety of these ingredients in animals has previously been reviewed (40 FR 12909 and 58 FR 46589). Therefore, this letter addresses only the 9 human studies, 8 of which were clinical studies. Because only a brief synopsis of each study was provided, we contacted you on May 2, 1995 to request additional information. You stated that the original data for these studies could not be located and no other information was available. Thus, your company was unable to provide information that would have enabled us to conduct a more thorough evaluation.

78N-036L

LET 90

The Office of OTC Drug Evaluation has reviewed your submission and determined that the data are insufficient to include the combination of bisacodyl and DSS in the final monograph for OTC laxative drug products. We have the following comments concerning your submission:

(1) The Weiss data were not a clinical trial but an early study in 1964 to determine the preferred dose that would be suitable for later clinical trials. It was found that the lower dose combination (bisacodyl 5 milligram (mg) and DSS 100 mg) was preferred by more of the 83 study subjects than the higher dose combination (bisacodyl 7.5 mg and DSS 100 mg) due to less cramping. No other details were available.

#### Double-Blind, Parallel Studies

(2) The Baer study (1967), conducted in 56 subjects (45 to 85 years old) with constipation and other concurrent illnesses (preferably cardiovascular diseases), compared the safety and efficacy of bisacodyl 5 mg and the combination of bisacodyl 5 mg and DSS 100 mg (bisacodyl/DSS) for relief of constipation. Subjects (28 in each group) were given 1 to 2 tablets of either treatment at bedtime for a total of 4 weeks. The efficacy variables measured were all subjective: global effectiveness (excellent/good/fair/poor) and the number of days that subjects considered themselves as having "adequate" bowel movement. Adequate was not defined in the report. Five subjects from each group dropped out due to abdominal pain or gripping. Therefore, data from only 23 subjects in each group were available for evaluation. The results showed no statistically significant difference between the two treatments.

There were much more cases ( $p < 0.05$ ) of adverse drug reactions (ADRs) (gripping and abdominal pain) reported in the bisacodyl group (48 events in 15 subjects) than the combination group (28 events in 14 subjects). The investigator concluded that the combination was slightly better than bisacodyl alone, although the difference did not reach statistical significance.

(3) The Landesman study (1967) was conducted in 199 post-partum subjects (17 to 47 years old) and compared bisacodyl with the bisacodyl/DSS combination for its laxative effects over 4 to 5 days. Treatments were given 12 hours post-partum and lasted an average of 4 days. Results showed no significant difference between the two treatments.

ADRs were mild. Five of the 101 subjects in the bisacodyl group and 4 of the 98 subjects in the combination group experienced slight gripping or abdominal pain. One subject in each group had diarrhea, and the subject in the bisacodyl group discontinued therapy because of the diarrhea. Rescue treatments (milk of

magnesia or soapsuds enema) were comparable in the two groups with 7 subjects in the bisacodyl group and 9 subjects in the combination group using the rescue therapy. The investigator stated that the duration of the study was too short for any benefit of DSS to be shown.

(4) The Dubow study (1967), a 6-week study conducted in 150 subjects (9 to 19 years old, 80% male) with a history of mild to moderate constipation, compared bisacodyl with the bisacodyl/DSS combination for laxative effect. There were 78 subjects in the bisacodyl group and 72 subjects in the combination group. During the first 2 weeks (phase-in period) of the study, no subjects received treatment. Baseline parameters were supposed to be established during this period, but no data were provided in the report. Each subject was then given 1 tablet of either treatment daily for the next 4 weeks. The efficacy parameters measured were similar to the Landesman study, i.e., global assessment and the number of subject days with adequate bowel movements. The report indicates that the combination was "slightly" better than bisacodyl alone, although only the analysis of one subparameter was statistically significant. While no subject reported any adverse event in the bisacodyl group, 15 subjects in the combination group reported 33 ADRs (14 had gripping/abdominal pain and 1 had itching). The report indicated that all reactions were mild and of no consequence.

The Office of OTC Drug Evaluation concludes that crucial data are missing from these studies: placebo-control, subject matching, randomization, inclusion/exclusion criteria, compliance, baseline laxation, dietary influences, activity level of subjects during the studies, concomitant medications, etc. Generally, if any statistical analyses were performed, only a p-value was given without specification of which statistical test was chosen. In addition, all studies used a global-type assessment to measure efficacy; however, most current laxative studies use several objective parameters (such as time to effect, consistency of stool, stool weight, stool water content, median strain during bowel movement, stool frequency per week, etc.) to measure efficacy. In addition, the Landesman study used an end-point of 4 to 5 days, while the other two studies used 4 weeks for the assessment of clinical efficacy. A 4-week endpoint does not correlate with the current directions that OTC laxatives be used for not more than 7 days. In addition, both the Baer and Landesman studies failed to demonstrate a statistical advantage of using the combination over bisacodyl alone. The Dubow study was not consistent, only one subparameter of all analyses was statistically significant. Although there were equivalent ADR profiles in the Baer and Landesman studies, the Dubow study showed that the combination product reportedly had a much higher incidence of side-effects compared to using bisacodyl alone (15 out of 72 versus 0 out of 78). Therefore, these studies do not support the approval of the combination.

Double-Blind, Crossover Studies

(5) The Friedman study (1967) compared bisacodyl with bisacodyl/DSS for laxative effect, each for 4 weeks, in 40 subjects (mean age about 60 years, 70 to 80% female). There was a very high dropout rate (reasons not given) with only 16 subjects (40 percent) completing the entire crossover. Efficacy parameters used were similar to previous studies in which subjects were asked at the end of the study about their general response and the number of days with adequate bowel movements.

For general (global) response, 10 out of 16 subjects (63 percent) reported that they were better on the combination compared to 2 out of 16 subjects (13 percent) on bisacodyl; 4 out of 16 (25 percent) stated that there were no differences. This difference was significant ( $p < 0.01$ , statistical test not listed). However, as for adequacy of response for subject-days, there were no differences between the two groups. In addition to the 16 subjects who completed the crossover, 10 other subjects completed half of the study. Seven took the combination and three took the bisacodyl for 4 weeks.

The investigators tried to re-analyze the data (not planned in the protocol) by adding the partial data of these 10 subjects to the data of the 16 subjects. The data were then re-analyzed as a parallel comparison assuming 23 subjects (16 plus the additional 7) in the combination group and 19 subjects (16 plus the additional 3) in the bisacodyl group. However, this secondary analysis did not alter the reported final outcome.

There was a fairly high incidence of ADRs. Fifteen out of 19 subjects on bisacodyl and 14 out of 23 subjects on the combination experienced abdominal pain and gripping. Two subjects on bisacodyl and one subject on bisacodyl/DSS dropped out due to these reactions. Five subjects on bisacodyl and six subjects on bisacodyl/DSS experienced other reactions such as diarrhea, gas pain, heartburn, nausea, headache, itching, diarrhea, etc.

(6) The Goldfarb study (1967), conducted in 30 subjects (mean age 75 years, 14 men and 16 women) with moderate to severe constipation, compared bisacodyl and bisacodyl/DSS for laxative effect, each for 4 weeks. There were two bisacodyl dropouts within 1 week because of diarrhea. An additional subject in the combination group was excluded because the subject took additional bisacodyl. However, by the time of dropout or exclusion, these subjects had completed most of the studies so their global responses were still recorded. Results showed that there were either no differences or that bisacodyl was better than the combination. Subjects were allowed to use any rescue laxative (another product) if constipation was not relieved by the study medications. Cascara, oral and rectal sodium

phosphate, soapsuds enema, mineral oil, milk of magnesia, and suppositories (type not stated) were used for rescue therapy. Many subjects used rescue therapy. Nineteen subjects in the bisacodyl group reported 105 uses of rescue laxative compared to 21 subjects in the combination group who reported 127 uses of rescue laxative during the study. Two subjects in the bisacodyl group also required catheterization. The investigators also attempted to do additional preference analysis on the two treatments. Slightly more subjects preferred bisacodyl over the combination; however, this was reported not to be statistically significant.

Many ADRs were reported in the bisacodyl group (39 events by 21 subjects) and the combination group (19 events by 10 subjects). Reported ADRs were gripping, abdominal pain, diarrhea, nausea and vomiting, gas pain, mucous in stool, and malodorous urine.

(7) The Puls study (1967), conducted in 30 subjects (18 to 96 years old, 13 men and 17 women), compared bisacodyl with bisacodyl/DSS for laxative effect, each over 28 days. All subjects had chronic constipation with some other chronic medical condition(s) such as heart or lung disease, cancer, etc. Only 24 subjects completed the crossover. Six subjects were dropouts: one due to no response, one due to side effects on both treatments, and four due to side effects on the combination product. Eight subjects on bisacodyl and nine subjects on the combination required rescue treatment with other laxatives. More ADRs were reported in the bisacodyl group (37 events by 4 subjects) than in the combination group (17 events by 5 subjects). The ADRs were gripping, abdominal pain, nausea, and loose stool.

Although, the analyses of the two primary efficacy variables were not significant, the investigators stated that of the 24 subjects that completed the crossover, 16 stated they did well on either treatment. Of the remaining 8 subjects, 7 stated they were better on the combination ( $p=0.035$ , by Sign test). Thus, the investigators concluded that the combination was better than bisacodyl.

The Office of OTC Drug Evaluation concludes that these studies (Friedman, Goldfarb, and Puls) are inadequate because they were not well-controlled (i.e., lack randomization, baseline laxation, etc.), contained no specified statistical analyses, and all endpoints were subjective. In addition, for crossover studies, there are additional concerns of carryover effect and treatment-by-period interaction. Further, dropouts were not included in the analyses and no baseline was reported. None of three studies mentioned any washout periods. The results are not convincing and the Friedman study had an extremely high (60 percent) dropout rate. The secondary analysis (to change the data from a crossover design to a parallel comparison) is also invalid. The

high incidence of ADRs in both the Friedman and Goldfarb studies and the liberal use of rescue therapies in the Goldfarb and Puls studies raise serious questions about reliability of the results

In addition, despite the claim of an apparent statistical advantage in some preference analyses in the Friedman and Puls studies, these reports were mainly secondary endpoints with the primary efficacy variables remaining statistically insignificant. In fact, based on the global response assessment, the Goldfarb study is a very negative study because 66 to 67 percent of the subjects rated had only poor/fair responses during either treatment and more subjects preferred bisacodyl over the combination.

### C. Open-label Studies

(8) The Orchow study (1967), an open-label, three-arm, crossover study conducted in 24 subjects, compared bisacodyl, DSS, and bisacodyl/DSS for laxative effect over 6 weeks. Subjects were chronically debilitated nursing residents with various medical diseases such as paralysis, multiple sclerosis, coronary artery disease, mental problems, etc. About 60 percent of the subjects were over 65 years of age. All subjects were given each treatment for 2 weeks and then switched over to the other treatment. There were no wash-out periods, however, the data on the first day of each treatment were not used to minimize possible carry-over effects. Four subjects dropped out at various times during the treatment; only one was reportedly due to a side-effect (abdominal pain on bisacodyl).

There were more ADRs (abdominal pain or gripping) in the DSS group compared to either the combination or the bisacodyl alone (44 versus 25 versus 24). Diarrhea was occasionally reported (exact number of events not provided) but not significantly different among the three groups. One subject on DSS and on the combination treatment complained about nausea; no subjects on bisacodyl complained.

(9) The Miller study (1967), an open-label, parallel study in 63 postoperative gynecologic subjects (16 to 72 years old), compared senna concentrate (187 mg) and bisacodyl/DSS for laxative effect over 2 to 23 days. Thirty-one subjects were assigned to the senna concentrate group and 32 subjects were assigned to the combination group. On the third day after surgery, 1 to 2 tablets of the combination or senna concentrate were given until the subjects were discharged. The average duration of treatment for the combination was 7.2 days and 6.9 days for senna concentrate. Twelve subjects on the combination and 11 subjects on senna concentrate received concurrent narcotics for pain control. Five subjects on senna concentrate also received soapsuds enema as rescue therapy compared to none on the combination ( $p=0.02$ , Fisher's Exact test). Results were

reported to show that the combination was slightly better than senna concentrate but not statistically significant by Chi-square.

More cases of ADRs were reported in the combination group (30 events in 22 subjects) than the senna concentrate group (18 events in 10 subjects). The ADRs were gripping, abdominal pain, nausea, loose stool, diarrhea, urinary retention, headache, dizziness, vertigo, and chills. Five subjects in the combination group and 4 subjects in the senna concentrate group dropped out due to ADRs.

The Office of OTC Drug Evaluation concludes that these studies (Orchow and Miller) have the same problems as the other studies discussed above. In addition, because these studies are unblinded, the usefulness of any subjective efficacy parameters (global and adequacy of bowel movement) is even more questionable. The Orchow study was a crossover study without a washout period. The sample size was relatively small, only 24 subjects, and there was a high dropout rate of 17 percent. The Miller study showed a worse ADR profile for the combination product (22 out of 32 subjects) compared to senna concentrate (10 out of 31 subjects).

The submitted studies do not meet acceptable standards for documenting the safety and efficacy of the bisacodyl/DSS combination for OTC laxative use. The studies were not placebo-controlled, and no details were provided regarding subject matching, randomization, inclusion/exclusion criteria, compliance, baseline laxation, dietary influences, activity level of subjects during studies, concomitant medications, predefined statistical analyses, etc. None of these studies evaluated the efficacy of the individual ingredients versus combination versus placebo. Only one study (Dubow) was said to have measured baseline laxation (results were not reported), and liberal use of rescue laxatives was frequently allowed without adjustment of results for this situation. Two studies were unblinded (Orchow and Miller), results of the blinded crossover studies contradicted each other (Puls and Goldfarb), two parallel, blinded studies showed no difference (Baer and Landesman), and the Weiss study was not set up to evaluate efficacy.

In addition, all the studies submitted used only a subjective assessment for efficacy. Most current laxative studies also use objective parameters (such as consistency of stool, stool weight, stool water content, median strain during bowel movement, stool frequency per week, time to effect, etc.) to assess efficacy. The labeled 7-day directions for OTC use and lack of such a predetermined endpoint in these studies is also of concern.

The Office of OTC Drug Evaluation intends to recommend to the Commissioner that the agency respond to your comments in the

above manner in the final monograph for OTC laxative drug products. If you wish to conduct a new study, we suggest that you submit a protocol addressing the above items before starting the study. It should be submitted in three copies, identified with the docket and comment numbers shown at the beginning of this letter, to the Dockets Management Branch (HFD-305), Food and Drug Administration, Room 1-23, 12420 Parklawn Drive, Rockville, MD 20857.

We hope this information will be helpful

Sincerely yours,



William E. Gilbertson, Pharm.D.  
Director  
Monograph Review Staff  
Office of OTC Drug Evaluation  
Center for Drug Evaluation and Research

Vincent De Stefano

Page 8

above manner in the final monograph for OTC laxative drug products. If you wish to conduct a new study, we suggest that you submit a protocol addressing the above items before starting the study. It should be submitted in three copies, identified with the docket and comment numbers shown at the beginning of this letter, to the Dockets Management Branch (HFD-305), Food and Drug Administration, Room 1-23, 12420 Parklawn Drive, Rockville, MD 20857.

We hope this information will be helpful.

Sincerely yours,



William E. Gilbertson, Pharm.D.  
Director  
Monograph Review Staff  
Office of OTC Drug Evaluation  
Center for Drug Evaluation and Research



## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

Martin M. Kaplan, M.D., J.D.  
Vice President,  
Drug Regulatory Affairs  
Boehringer Ingelheim  
900 Ridgeburg Road  
P.O. Box 358  
Ridgefield, Connecticut 06877-0358

FEB 16 2000

Re: Docket No. 78N-036L  
Comment No. RPT 14

Dear Dr. Kaplan:

Reference is made to your submission dated October 21, 1999, identified as Comment No. RPT 14, under Docket No. 78N-036L in the Dockets Management Branch, entitled "A Six Month Oral Gavage Carcinogenicity Study of Bisacodyl in the Heterozygous p53 Transgenic Mouse (Study No. 98R027)." This study was submitted to support the safety of bisacodyl as a Category I (safe and effective) over-the-counter (OTC) laxative drug ingredient.

We have the following comments on the study:

In the first week of treatment, heterozygous p53 transgenic mice received bisacodyl by oral gavage at doses of 0, 800, 4000, and 8000 mg/kg/day. The high dose of 8000 mg/kg/day was given as two daily doses of 4000 mg/kg administered 4 hours apart. Based upon recommendations received from the FDA's Center for Drug Evaluation and Research Carcinogenicity Assessment Committee (CAC), the mid dose was changed from 4000 to 2000 mg/kg/day and the low dose was changed from 800 to 500 mg/kg/day at the beginning of the second week of treatment. A positive control group received p-cresidine at 400 mg/kg/day.

There were no treatment-related findings of hyperplasia, metaplasia, or tumors for heterozygous p53 transgenic mice that received bisacodyl.

For heterozygous p53 transgenic mice that received the positive control, p-cresidine, neoplastic findings were observed in the urinary bladder that included transitional cell papilloma and

Martin Kaplan, M.D., J.D.

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carcinoma for 4 of 30 (13.3 percent) of the animals. Additional findings in the urinary bladder included transitional epithelial hyperplasia for 26 of 30 (86.7 percent) of the animals, squamous metaplasia for 11 of 30 (36.7 percent) of the animals, transepithelial apoptosis for 13 of 30 (43.3 percent) of the animals, and spindle cell hyperplasia for 4 of 30 (13.3 percent) of the animals. The combined incidence of transitional cell papilloma, carcinoma, and hyperplasia, as well as squamous metaplasia, was 86.7 percent (26 of 30) of the animals.

For all groups including the control, undifferentiated sarcomas were observed in association with transponder identification chips. Survival rates were unaffected by treatment with bisacodyl. Body weight gain for female mice that received bisacodyl at 8000 mg/kg/day was impaired by >10 percent; however, final body weight was 94.2 percent of the control. Body weight gain and final body weight for male mice that received p-cresidine were impaired by >10 percent. Food consumption over the treatment period was significantly reduced for male and female mice that received p-cresidine. Bisacodyl treatment produced no increases in the frequency of micronuclei/polychromatic erythrocytes (PCE) in the peripheral blood. Bisacodyl at 8000 mg/kg/day produced centrilobular hepatocellular hypertrophy characterized by the presence of enlarged cells with abundant eosinophilic cytoplasm in female mice.

Based on our review of your submission and other information available for bisacodyl (refer to our letters dated April 8, 1998 and March 23, 1999, coded as LET175 and LET180, respectively, filed under Docket No. 78N-036L in the Dockets Management Branch), we conclude the following:

1. The results of the carcinogenicity study with bisacodyl in heterozygous p53 transgenic mice are acceptable.
2. Bisacodyl at oral doses up to 8000 mg/kg/day was not found to be tumorigenic in heterozygous p53 transgenic mice.
3. Based on currently available information, no further carcinogenicity testing of bisacodyl is recommended. The totality of the data available do not suggest a human carcinogenic risk from bisacodyl when used as recommended.

Martin Kaplan, M.D., J.D.

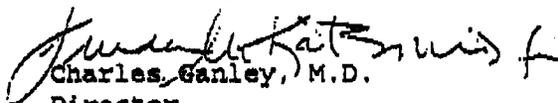
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Therefore, the data support the safety of bisacodyl as a Category I OTC laxative ingredient. The Division of OTC Drug Products intends to recommend to the Commissioner that the Agency respond to your submission in the above manner in an amendment to the final monograph for OTC laxative drug products.

Any comment you wish to make on the above information should be submitted in three copies, identified with the docket and comment numbers shown at the beginning of this letter, to the Dockets Management Branch (HFA-305), Food and Drug Administration, room 1061, 5630 Fishers Lane, Rockville, MD 20852.

We hope this information will be helpful.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Charles Ganley".

Charles Ganley, M.D.

Director

Division of OTC Drug Products

Office of Drug Evaluation V

Center for Drug Evaluation and Research

**Boehringer Ingelheim GmbH**

a member of

**Boehringer  
Ingelheim**



D-55216 Ingelheim

**CLINICAL TRIAL REPORT**

**Doc. No.:**

U98-0150

**BI Trial No.:** 122.51 (ASM 93/1)

**Test Substance(s):** Bisacodyl, 4,4'-diacetoxy-diphenyl-(pyridy-2)-methane (-bisacodyl),  
Dulcolax®

**Title:** Comparative Safety and Efficacy of Bisacodyl Sugar-coated Tablets in  
the Treatment of Constipation

**Clinical Phase:** IV

**GCP Compliance:** yes

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**Date of Report:** July 30, 1997

**Dates of Trial:** from May 14, 1994 to August 15, 1994

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**Confidential**

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3. SYNOPSIS AND TRIAL ABSTRACT

3.1 SYNOPSIS

Name of company: <b>Boehringer Ingelheim</b>		Tabulated Study Report		(For National Authority Use only)
Name of finished product: <b>Bisacodyl</b>		Page:	Number:	
Name of active ingredient: 4,4'-diacetoxy-diphenyl-(pyridyl-2)-methane (-bisacodyl)				
Ref. to Documentation:	Volume:	Page: to	Addendum No.:	
Report date: July 30, 1997	Number:	Study period (years): 1 5/94-8/94		
Title of study:	Comparative Safety and Efficacy of Bisacodyl Sugar-coated Tablets in the Treatment of Constipation			
Investigator:	Dr. med. von Behren, Dr. med. S. Berger, Dr. med. Degel, Dr. med. Herrmann, Dr. med. K.-D. Herzog, Dr. med. Mulverstedt, Dr. med. Najman, Dr. med. H.-J. Reimann, Dr. med. L. Schinke and Dr. med. U. Walther			
Study centre(s):	Wiesbaden, Wiesbaden, Offenbach, Frankfurt, Wiesbaden, Giessen, Frankfurt, Wiesbaden, Giessen and Wiesbaden			
Publication (reference):	None			
Clinical phase:	Phase IV			
Objective:	To assess the safety and efficacy of Bisacodyl sugar-coated tablets versus placebo in the treatment of constipation.			
Methodology:	Following a three day run-in period, patients were randomly assigned to receive either bisacodyl 5 mg sugar-coated tablets, to be taken at a dose of 10 mg once daily immediately prior to bedtime for three days, or matching placebo tablets to be taken once daily immediately prior to bedtime for three days. Patients recorded the frequency and consistency of bowel movements in daily diaries to assess the effectiveness of bisacodyl on a daily basis. The safety of bisacodyl was evaluated through the assessment of adverse events and by monitoring any clinically significant changes in laboratory values or physical examination findings. The investigator performed a global assessment of efficacy and of tolerance through patient questioning.			
No. of subjects entered: total: each treatment:	55 patients entered (28 bisacodyl, 27 placebo) 54 patients treated 27 patients bisacodyl; 27 patients placebo			
Diagnosis and main criteria for inclusion:	Patients diagnosed with constipation, defined as acute and habitual constipation and who met other entrance criteria.			
Test product: dose: mode of admin.: batch no.:	bisacodyl 5 mg sugar-coated tablets taken orally once daily immediately prior to bedtime for three days at a dose of 10 mg/day 30902			
Duration of treatment:	3 days.			

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<b>Reference therapy:</b> dose: placebo tablets mode of admin.: taken orally once per day immediately prior to bedtime for 3 days batch no.: 30703				
<b>Criteria for evaluation:</b> <b>Efficacy:</b> The criteria for efficacy were based on the evaluation of the primary efficacy variables, frequency of bowel movements and stool consistency compared to baseline. Patients were to record in daily diaries the number of bowel movements per day and the consistency of stools, for which days 0, 1 and 2 were the baseline period and days 2, 3 and 4 were the treatment period. For each bowel movement patients rated the consistency of their stools as either liquid, soft, well formed or hard. In addition, the investigator performed a global assessment of efficacy which was used as a secondary efficacy assessment. Each investigator provided a 4-step evaluation of severity of constipation by rating the frequency of bowel movements and consistency of stools on Study Day 5 in comparison to Study Day 2 using the following scale: worsened = worsening of either number of bowel movements or consistency of stools while the other either worsened or remained unchanged; unchanged = number of bowel movements and consistency of stools remained unchanged; somewhat improved = improvement of either number of bowel movements or consistency of stools while the other remained unchanged; significantly improved = improvement in both number of bowel movements and consistency of stools.  <b>Safety:</b> Patients were to record daily the occurrence of any adverse events in their diary. In addition to these events, any adverse events elicited in questioning by the investigator were recorded in the case report form. The investigator was to assess and record any adverse event in detail on the adverse events case report form including: the date and time of onset, description, severity, duration and outcome, etiology, relationship of the adverse event to the study drug, and action taken. The severity of adverse events was graded as mild, moderate or severe. The relationship of the adverse event to the study drug was assessed as concurrent condition, remote, possible, probable or definite. Laboratory tests were performed at baseline (Visit 2) and end of treatment (Visit 3) and all laboratory values considered clinically significantly abnormal by the investigator were recorded.				

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Report date: <b>July 30, 1997</b>	Number:	Study Period (years): <b>1</b> <b>5/94-8/94</b>		
<b>Statistical methods:</b>				
<b>Sample Size</b>				
Under the assumption that at least 80% of the patients treated with bisacodyl will show improvement of their constipation symptoms, a sample size of 22 (28) patients per treatment arm will provide 80% power to detect a treatment difference of 40% (35%) vs placebo with a two-sided test at the 0.05 level of significance.				
<b>Efficacy Variables</b>				
<b>Primary Efficacy Variables</b>				
<u>Number of Bowel Movements</u> - The total number of bowel movements per day was calculated for each patient. The average daily number of stools over the treatment period was calculated;				
<u>Consistency of Stools</u> - Patients were asked to record the consistency of each stool as being liquid, soft, well formed, moderately hard, or hard on the patient diary. The following scores were used: liquid = 1, soft = 2, well formed = 3, moderately hard = 4, and hard = 5. The amount of stools of each type was calculated for each patient. A daily stool consistency score was obtained by multiplying the number of stools of each consistency class by the appropriate score and dividing by the total number of stools that day. Stool consistency scores for the baseline treatment periods were computed by the analogous calculation.				
Changes from baseline to treatment in the daily number of stools and in stool consistency score were analyzed with ANOVA. The poolability of the by-center results was tested with the F-test for the interaction term from an ANOVA model with treatment, center, and treatment by center interaction effects at the 0.10 level of significance. If the interaction effect was not significant it was dropped from the model and the two-way main effects model was used to make treatment comparisons.				
<b>Secondary Efficacy Variables</b>				
<u>Investigator's Global Assessment of Efficacy</u> - The 4-step evaluation of severity of constipation (worsened, unchanged, somewhat improved, significantly improved) provided by the investigator was used as a secondary efficacy assessment;				
<u>Number of Bowel Movements and Consistency of Stools</u> - The number of bowel movements and the average of stool consistencies was summarized by treatment group for each study day with descriptive statistics including the mean, median, standard deviation and range.				
The investigator's global assessment of efficacy was analyzed with a Mann Whitney test.				
<b>Safety</b>				
Safety was analyzed throughout the course of this study by monitoring the occurrence of adverse events and changes in laboratory variables (including serum electrolyte levels). All patients who took at least one tablet were eligible for safety data analysis. The incidence of adverse events was summarized by treatment group with patient counts and percents. The number of patients reporting clinically significant shifts in serum electrolytes and other laboratory parameters was summarized by treatment group. Statistical treatment comparisons for adverse events and changes in laboratory variables were made using Fisher's exact test.				

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<b>SUMMARY - CONCLUSIONS:</b>				
<p><b>Efficacy results:</b>          The primary efficacy analysis for mean stool number and consistency over the three day study period indicated the value for mean stool count for the bisacodyl treatment group (median = 1.5) was statistically significantly (<math>p = 0.003</math>) greater than that for the placebo group (median = 0.8). Stool consistency was also improved in favor of the active treatment. The median stool consistency value was 2.4 on bisacodyl and 4.5 on placebo (<math>p = 0.001</math> using the CMH test stratified for baseline consistency). Analysis of the secondary efficacy variables indicated there was a significant difference in global efficacy (<math>p = 0.045</math>) with median values of 1.0 (significant improvement) for the bisacodyl treatment group and 2.5 (value between somewhat improved and unchanged) for the placebo group.</p> <p><b>Safety results:</b>          Of the 27 bisacodyl treated patients who were eligible for the safety analysis, 15 (55.6%) reported a total of 37 adverse events. By comparison 18 (66.7%) of the placebo patients reported a total of 29 adverse events. The most frequently reported adverse events actually representing laboratory abnormalities (10/26, 38.5%, bisacodyl; 11/25, 44.0%, placebo) were white cell and reticuloendothelial system disorders (mild leukocytosis). Other frequently reported adverse events were gastro-intestinal (4/26, 15.4%, bisacodyl; 5/25, 20%, placebo), metabolic and nutritional (3/26, 11.5%, bisacodyl; 2/25, 8.0%, placebo), urinary system disorders (3/26, 11.5%, bisacodyl; 1/25, 4.0%, placebo) and liver and biliary system disorders (1/26, 3.8%, bisacodyl; 2/25, 8.0%, placebo). All of the adverse events reported on bisacodyl were rated mild in intensity; two events reported on placebo were rated as moderate (<math>p = 0.107</math>) and the remainder as mild. No patient deaths occurred, and no adverse events occurred which were serious, severe or resulted in discontinuation of the study drug. All of the adverse events could be easily tolerated and were clinically not relevant. There was no significant difference between the treatment groups with regard to the global tolerance score. Few clinically relevant laboratory observations were noted and no clinically significant differences were noted between treatment groups. With the assessment of patients' vital signs there was no evidence of untoward effects caused by bisacodyl.</p> <p><b>Conclusions:</b>          In this double blind, multicenter, parallel comparison between two groups of 27 patients randomly assigned to receive either bisacodyl or placebo, bisacodyl was significantly better than the placebo in relieving constipation. The value for mean stool count for the bisacodyl treatment group (median count = 1.5) was statistically significantly (<math>p = 0.003</math>) greater than that for the placebo group (median count = 0.8). Stool consistency was also improved in favor of the active treatment. The median stool consistency value was 2.4 on Bisacodyl and 4.5 on placebo (<math>p = 0.001</math> using the CMH test stratified for baseline consistency). The patients on bisacodyl reported more adverse events (37) compared to placebo (29). However, no particular pattern of side effects emerged as being more likely to occur on the active treatment compared to placebo.</p>				