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Food and Drug Administration  
Rockville MD 20857

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1050 Connecticut Avenue, NW  
Washington, DC 20036-5339

CFR 2

Re: Docket No. 78N-036L  
Comments No. CP0007  
and AMD0003

Dear Mr. Reichertz:

This letter concerns your citizen petition (coded CP0007) submitted on behalf of the C. B. Fleet Company, Inc., dated November 12, 1987 and filed with the Dockets Management Branch on November 13, 1987. The petition requested that the tentative final monograph on OTC laxative drug products be amended to include an enema dosage form for the ingredient bisacodyl and to provide for its use as a post-evacuant in conjunction with a barium enema.

In my letter of January 12, 1988, I informed you that we were in the process of evaluating your petition and that additional data were needed for us to complete our evaluation. On May 17, 1988 you provided the additional data requested in my letter. This submission was coded AMD0003 by the agency.

We have completed our review and determined that a 10-mg dose of bisacodyl (administered in a 37.5 milliliter (mL) aqueous suspension rectal enema formulation) is safe and effective for use by adults and children 12 years of age and over, but that safety in children under 12 years of age and effectiveness as a post-evacuant at any age have not been demonstrated.

We have the following specific comments regarding the studies that were submitted:

The study by Salen and Keating compared two dosages of a bisacodyl enema with a bisacodyl suppository and a bisacodyl microenema. One hundred and four patients (101 male, 3 female, ages 24-88) were entered in the study; 96 patients were evaluated. One enema unit or one suppository was given to each patient 1 to 3 hours prior to the examination. Evaluation criteria included the time to first response, the number of bowel movements, the presence or absence of abdominal or other discomfort, and the adequacy of preparation for proctoscopic examination.

Fifty-nine percent of the patients (13 out of 22) who received the bisacodyl enema responded within 15 minutes compared with a

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32-percent response within 15 minutes for the patients (8 out of 25) who received the bisacodyl suppository and a 38-percent response for the patients (9 out of 24) who received the bisacodyl microenema. Seventy-three percent of the bisacodyl enema patients (16 out of 22) were rated as having adequate bowel preparation for proctoscopic examination compared with ratings of 72 percent (18 out of 25 patients) and 71 percent (17 out of 24 patients), respectively, for the bisacodyl suppository and the bisacodyl microenema.

Based on the above, the agency has determined that only the criterion "time to response" provides information suggesting that the bisacodyl products can be differentiated from one another. Because a vehicle control was not used, this complicates interpretation of the results. Further, the bisacodyl enema formulation tested is somewhat different from the marketed formulation. The sponsor concludes that the glycerin and methylcellulose in the enema formulations do not individually contribute to the laxative effect of the product. While the quantities of each ingredient probably do little, we do not know their effect in combination.

The question to be addressed by the study is not the laxative activity of bisacodyl, but whether an enema formulation is as effective as a suppository formulation of this ingredient in producing laxation. Based on the 59-percent patient response rate within 15 minutes for the bisacodyl enema and the 32-percent patient response rate for the bisacodyl suppository control group, we find that the study, although qualitative and not optimally designed, provides substantial evidence that the enema containing 10 milligrams (mg) bisacodyl in a 37.5 mL aqueous suspension is at least as effective as, and can be substituted for, the 10-mg bisacodyl suppository.

The study by Swerdlow consisted of administration of one unit of bisacodyl enema (containing 10 mg in 37.5 mL) to each of 20 hospitalized or office subjects from 1 to 3 hours prior to proctoscopic examination. The same evaluation criteria as in the Salen and Keating study were used. The study showed a 90-percent response rate with a mean time of 10 minutes to first response after the administration of the bisacodyl enema. The bowel preparation was rated as adequate for 95-percent (19 out of 20) of the patients. Cramping was reported in 10 percent of the patients (2 out of 20). Although this study was uncontrolled, its favorable results are of value primarily as support for the results of the Salen and Keating study.

The study by Kaye and Solomon is a report on the use of bisacodyl in propylene glycol as an additive to barium enema suspensions. Twenty mg of bisacodyl was used in 109 cases and 10 mg was used in an additional 39 cases. Although the authors report bisacodyl in propylene glycol enema useful as an addition to the barium suspension, the study is uncontrolled and involves a bisacodyl formulation and dose different from that proposed in your petition. Therefore, this study does not provide substantial evidence to support the use of the proposed bisacodyl enema formulation as a post-evacuant in conjunction with a barium enema.

The study by Magilner and Ostrum was a randomized, double-blind trial in 200 patients scheduled to undergo barium enema procedures in which the effectiveness of bisacodyl enema was compared with Clysodrast<sup>R</sup> enema (3 mg of bisacodyl and 5 gm of tannic acid in 1400 mL of water) as a post-evacuant for barium enemas. The evaluation of drug efficacy was based on the post-evacuant film for:

- a) Final diagnosis after barium enema,
- b) Overall impression of the test material as a post-evacuant (excellent, good, fair, or poor),
- c) Overall impression of the test material's ability to improve the mucosal pattern (excellent, good, fair, or poor).

While there was little difference between bisacodyl (72 percent of tests rated excellent) versus Clysodrast<sup>R</sup> (70 percent of tests rated excellent) as post-evacuants, bisacodyl scored poorly on its ability to improve the mucosal pattern. Only 7 percent of the bisacodyl patients (7 out of 100) were rated as excellent in improvement of the mucosal pattern following its use as a post-evacuant, while 79 percent of the patients (79 out of 100) were rated as showing fair or poor improvement. By comparison, 53 percent of the Clysodrast<sup>R</sup> patients (53 out of 100) were rated as excellent in improvement of the mucosal pattern with only 27 percent (27 out of 100) rated as showing fair or poor improvement. There were no differences in patient complaints between the groups; 84 percent of the patients had no complaints.

On the basis of this study, we cannot conclude that bisacodyl enema is safe and effective as a post-evacuant for barium enema. It does not appear to be as effective for improving the mucosal pattern as the approved Clysodrast<sup>R</sup>. The usefulness of a post-evacuant is not merely to get rid of barium after a procedure, but to add to the radiologist's ability to assess

colonic pathology. On the post-evacuant film, with or without air contrast, mucosal integrity may be better defined, so that diagnostic accuracy is enhanced. This is the case with Clysodrast<sup>R</sup>, but not with the bisacodyl formulation used in this study. We, therefore, cannot conclude, on the basis of the data provided, that bisacodyl enema is effective as a post-evacuant for barium enema.

Based on the data provided, we are able to conclude that 10 mg of bisacodyl administered in a 37.5 mL aqueous suspension rectal enema formulation can be generally recognized as safe and effective as a laxative for adults and children 12 years of age and over. Effectiveness as a post-evacuant in conjunction with a barium enema has not been demonstrated on the basis of the information provided. The safety and effectiveness of the formulation as either a laxative or as a post-evacuant has also not been demonstrated for children under 12 years of age because no studies in children were submitted. Use of this bisacodyl enema formulation as part of a bowel cleansing system is addressed in my other letter to you of this date.

Based on the above, we plan to recommend to the Commissioner that proposed 21 CFR 334.60(c)(1)(ii) be changed to read "Rectal dosage forms" from the currently proposed "Rectal suppository dosage forms," and that the following be added to proposed 21 CFR 334.60(d)(2):

Rectal enema dosage: Adults and children 12 years of age and over: 10 milligrams bisacodyl in 37.5 milliliters of aqueous suspension in a single daily dose. Children under 12 years of age: Consult a doctor.

The Division of OTC Drug Evaluation intends to recommend to the Commissioner that the agency respond to your petition in the above manner in the final monograph for OTC laxative drug products, which will be published in a future issue of the FEDERAL REGISTER. Following that publication, you may file a citizen petition to amend the final monograph or file a new drug application for the post-evacuant claim for bisacodyl enema, as well as for its use as a laxative in children under 12 years of age.

Any comment you may wish to make on the above information should be submitted in three copies, identified with the docket

number shown at the beginning of this letter, to the Dockets Management Branch (HFA-305), Food and Drug Administration, Room 4-62, 5600 Fisher Lane, Rockville, MD 20857.

Sincerely yours,

A handwritten signature in black ink, appearing to read "W. E. Gilbertson". The signature is written in a cursive, somewhat stylized script.

William E. Gilbertson, Pharm. D.  
Director

Division of OTC Drug Evaluation  
Office of Drug Standards  
Center for Drug Evaluation and Research