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Washington, DC 20036-5339

OCT 26 1989

Re: Docket No. 78N-036L  
Comments No. CP0008  
and SUP005

Dear Mr. Reichertz:

This letter concerns your citizen petition (Coded CP0008) submitted on behalf of the C. B. Fleet Company, Inc., dated November 12, 1987, and filed under Docket No. 78N-036L in the Dockets Management Branch on November 13, 1987. The petition requested that the tentative final monograph for OTC laxative drug products (published in the FEDERAL REGISTER of January 15, 1985; 50 FR 2124) be amended to include 6 additional bowel cleansing systems.

In my letter of May 16, 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 August 16, 1988 you provided the additional data requested in my letter. This submission was coded SUP005 by the agency.

We have completed our review and determined that two of the proposed bowel cleansing systems are safe and effective for use by adults and children 12 years of age and over. The other four proposed bowel cleansing systems require additional data to demonstrate their safety and effectiveness.

We have the following specific comments regarding each of the six bowel cleansing systems and the data submitted in support of them:

Kit Number 1: A kit containing the following 3 laxative drug products for sequential administration: 7.56 grams (g) of sodium phosphate and 20.2 g of sodium biphosphate in oral solution, 20 milligrams (mg) of bisacodyl administered orally at least 3 hours after administration of the sodium phosphate/sodium biphosphate oral solution, 10 mg of bisacodyl administered by suppository at least 9 hours after the administration of the oral bisacodyl and at least 1 hour before the scheduled x-ray or examination.

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Kit number 1 substitutes 7.56 g of sodium phosphate and 20.2 g of sodium biphosphate for 25 g of magnesium citrate in the bowel cleansing system listed in § 334.32(a) of the OTC laxative tentative final monograph (50 FR 2153). It also slightly alters the current dosing regimens of oral and rectal bisacodyl from 15-20 mg bisacodyl orally 2 hours after magnesium citrate to 20 mg bisacodyl at least 3 hours after sodium phosphate/sodium biphosphate, and from 10 mg bisacodyl suppository 9 hours after oral bisacodyl and at least 2 hours before the x-ray to at least 9 hours after the oral bisacodyl and at least 1 hour before the x-ray. The proposed bowel cleansing system containing these dosages and regimen has been marketed for over 15 years.

Both magnesium citrate and sodium phosphate/sodium biphosphate are listed in the OTC laxative tentative final monograph as single ingredient Category I saline laxatives, and the dosages in the bowel cleansing systems would be the maximum single daily dose permitted for each. In addition, in § 334.80 professional labeling claims have been proposed for both magnesium citrate and sodium phosphate/sodium biphosphate for use as part of a bowel cleansing regimen in preparing the patient for surgery, x-ray, and endoscopy (50 FR 2157). The data provided included a summary report of a clinical evaluation of kit no. 1 compared to Evac-Q-Kit, a bowel cleansing system listed in § 334.32(b) of the OTC laxative tentative final monograph (50 FR 2153) and consisting of magnesium citrate, phenolphthalein, and a carbon dioxide-releasing suppository.

In this single blind randomized study of 108 patients being prepared for barium enema, 57 patients received kit number 1 and 51 patients received Evac-Q-Kit. Thirty-one percent of the patients treated with kit number 1 showed moderate to extensive gas retention after treatment compared with 53 percent of the patients treated with Evac-Q-Kit. Seventy five percent of the patients treated with kit number 1 showed good to excellent mucosal detail on examination compared to 54 percent of the patients treated with Evac-Q-Kit. Overall evaluation (satisfactory/unsatisfactory) of the colon preparation showed no significant difference between the two bowel cleansing systems. There were no significant differences in side effects produced by the two kits.

Although this study does not provide a comparison between kit number 1 and the most similar bowel cleansing system (magnesium citrate followed by bisacodyl), it does compare another Category I bowel cleansing system (magnesium citrate, phenolphthalein, and carbon dioxide-releasing suppositories, (§ 334.32(b), 50 FR 2156) with one in which sodium

phosphate/sodium biphosphate is substituted for magnesium citrate. The results of this study, together with other data already considered by the agency in the laxative tentative final monograph (50 FR 2137), support the contention that sodium phosphate and sodium biphosphate can be interchanged for magnesium citrate safely and effectively in a Category I bowel cleansing system. This interchangeability would apply to either of the bowel cleansing systems specified in proposed § 334.32 in the OTC laxative tentative final monograph (50 FR 2153). The safety and effectiveness of the dose and dose regimen proposed for kit number 1 are supported by previous agency findings in the tentative final monograph and by the data provided. Appropriate additions to § 334.32 will be included in the final monograph.

Kit Number 3: A kit containing the following 3 laxative drug products for sequential administration: 7.56 g of sodium phosphate and 20.2 g of sodium biphosphate in oral solution, 20 mg of bisacodyl administered orally at least 3 hours after administration of the sodium phosphate/sodium biphosphate oral solution, 10 mg of bisacodyl administered by enema 9 hours after the administration of the oral bisacodyl and at least 1 hour before the scheduled x-ray or examination.

This kit is identical to kit number 1 except for the substitution of a 10 mg bisacodyl enema for the 10 mg bisacodyl suppository. As discussed in my other letter to you of this date, we concur that the submitted data support the substitution of the 10 mg bisacodyl enema formulation for the Category I 10 mg bisacodyl suppository.

We therefore concur that a Category I bowel cleansing system substituting a 10 mg bisacodyl enema for a 10 mg bisacodyl suppository is acceptable. Appropriate additions to § 334.32 will be included in the final monograph.

Kit Number 2: A kit containing the following 3 laxative drug products for sequential administration: 7.56 g of sodium phosphate and 20.2 g of sodium biphosphate in oral solution, 20 mg of bisacodyl administered orally at least 3 hours after administration of the sodium phosphate/sodium biphosphate oral solution, and administration of a large volume liquid castile soap enema at least 9 hours after administration of the oral bisacodyl and at least 2 hours before the scheduled x-ray or examination.

Bowel cleansing kit number 2 is the same as bowel cleansing kits 1 and 3 except for the substitution of a soap enema in place of the bisacodyl suppository or bisacodyl enema. As noted in your submission of August 16, 1988 (SUP005), no

clinical studies of the liquid castile soap enema have been performed, although some textbooks of the 1940s and 1950s do refer to soap water enemas. No data on soap water enemas have been submitted to the OTC drug review and such products are not discussed in the OTC laxative tentative final monograph (50 FR 2124). In view of the literature reports noted in your own submission that soap enemas have caused adverse reactions and are irritating, as well as the lack of clinical data on their safety and effectiveness, there is no adequate basis to recommend approval of kit number 2 or any bowel cleansing kit containing a soap enema. Should the company wish to pursue approval of kits containing a soap enema, well-controlled clinical trials comparing a bowel cleansing kit with a soap enema to that with a bisacodyl enema or suppository will be necessary.

Kit Number 4: A kit containing the following 3 laxative drug products for sequential administration: 60 milliliters (mL) of castor oil emulsion in oral solution, 20 mg bisacodyl administered orally at least 3 hours after administration of the castor oil emulsion in oral solution, 10 mg of bisacodyl administered by suppository at least 9 hours after the administration of the oral bisacodyl and at least 1 hour before the scheduled x-ray or examination.

Proposed bowel cleansing kit number 4 is the same as kit number 1 but substitutes castor oil for sodium phosphate and sodium biphosphate. Castor oil is in Category I in the OTC laxative tentative final monograph both as a stimulant laxative and for use alone in preparing the colon for endoscopic examination. There is no discussion in the laxative tentative final monograph regarding the use of castor oil with other laxatives as part of a bowel cleansing regimen. The proposed combination in kit number 4 would combine two stimulant laxatives rather than a saline laxative and a stimulant laxative. Such a substitution must be supported by adequate clinical data. The argument that because each ingredient proposed for kit number 4 is separately approved for bowel cleansing in the OTC laxative tentative final monograph, the combination must be safe and effective as a bowel cleansing system is not in keeping with the agency's guidelines on OTC combination drug products. The discussion of FDA's combination policy in comment 88 in the laxative tentative final monograph clearly states that "data are necessary to establish the safety and effectiveness of other specific combinations or to demonstrate that the specific ingredients in a pharmacological class are chemically and pharmacologically interchangeable." (See 50 FR 2146.)

The study by Strates and Hofmann (Pharmatherapeutica, 5:57-61, 1987) was a single-blind randomized study of 195 patients being prepared for barium enema, in which one group of patients received 2 ounces (oz) of castor oil followed by tap water enemas, while the other group received magnesium citrate, phenolphthalein, and a bisacodyl suppository. This study did not demonstrate any significant differences between the two bowel cleansing systems, although some significant differences were noted in patient preference for the magnesium citrate-containing kit. The authors of this study also noted that a previous study by Irwin et al. (Gastroenterology, 67: 47-50, 1974) found that a bowel preparation kit containing magnesium citrate, phenolphthalein, and a carbon dioxide-releasing suppository gave significantly superior results in preparing patients for barium enema than did 2 oz of castor oil followed by cleansing enemas. Neither of the aforementioned studies provide the support needed to establish the safety and effectiveness of a bowel cleansing kit containing castor oil followed by a cleansing tap water enema, nor do these data support the safety and effectiveness of a kit containing castor oil followed by oral bisacodyl and a soap water enema (kit number 5), or castor oil followed by oral and then rectal bisacodyl (kit number 6).

It is not possible to predict whether the castor oil-containing kits would produce results equivalent to, better than, or worse than the magnesium citrate bowel cleansing systems currently proposed as Category I in the laxative tentative final monograph. Such a kit would contain only stimulant laxatives, and the repetitive administration of such active agents may not be needed and may cause an increase in adverse reactions. Data from well-controlled clinical studies comparing castor oil to magnesium citrate would be necessary for further evaluation of these proposed kits, and for the castor oil kit containing soap enema, a separate evaluation, as noted above for proposed kit number 2, would be necessary.

Kit number 5: A kit containing the following 3 laxative drug products for sequential administration: 60 mL of castor oil emulsion in oral solution, 20 mg bisacodyl administered orally at least 3 hours after administration of the castor oil emulsion in oral solution, and administration of a large volume liquid castile soap enema (2/3 fluid oz of liquid castile soap) at least 9 hours after the administration of the oral bisacodyl and at least 2 hours before the scheduled x-ray or examination.

The deficiencies discussed for proposed kits number 2 and number 4 above apply equally to this proposed bowel cleansing system.

Kit number 6: A kit containing the following 3 laxative drug products for sequential administration: 60 mL of castor oil emulsion in oral solution, 20 mg of bisacodyl administered orally at least 3 hours after administration of the castor oil emulsion in oral solution, 10 mg of bisacodyl administered by enema at least 9 hours after the administration of the oral bisacodyl and at least 1 hour before the scheduled x-ray or examination.

The deficiencies mentioned in the discussion of proposed kit number 4 above apply equally to this proposed kit.

The Division of OTC Drug Evaluation is therefore proposing that the following bowel cleansing systems (identified as kit numbers 1 and 3 above) be included as Category I for adults and children 12 years of age and over in the final monograph for OTC laxative drug products:

A kit containing the following 3 laxative drug products for sequential administration: sodium phosphate/sodium biphosphate marketed as an oral solution identified in § 334.16(d) and bisacodyl identified in § 334.18(b) in both an oral dosage form and a suppository dosage form. (Kit number 1)

A kit containing the following 3 laxative drug products for sequential administration: sodium phosphate/sodium biphosphate marketed as an oral solution identified in § 334.16(d) and bisacodyl identified in § 334.18(b) in both an oral and an enema dosage form. (Kit number 3)

Please note that the dosage schedules for these kits will be included in § 334.66(d) in the final monograph and an appropriate cross-reference will be included in the above kit descriptions when included in § 334.32 of the final monograph.

The submitted data are insufficient to support the inclusion of your other proposed bowel cleansing kits (identified as kit numbers 2, 4, 5, and 6 above) as Category I at this time. Therefore, we are not proposing that any of those bowel cleansing systems be included in the OTC laxative final monograph.

The Division of OTC Drug Evaluation intends to recommend to the Commissioner that the agency respond to your comment 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 any of the kits not included in the monograph. Should the company wish to perform the clinical studies needed for any of these other kits, the agency would be glad to review proposed protocols.

Peter S. Reichertz, Esq.

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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 Fishers Lane, Rockville, MD 20857.

We hope this information will be helpful.

Sincerely yours,



William E. Gilbertson, Pharm. D.  
Director  
Division of OTC Drug Evaluation  
Office of Drug Standards  
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