LABORATORIES · INC
Braintree

December 10, 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Rockville, MD 20852

Re: Docket No. 78N-036L: Comment on Citizen Petition 1978N-0036L/CP28

Dear Sir or Madam:

On June 25, 2003 a Citizen Petition requesting that FDA modify the Tentative Final Monograph on Laxative Drug Products for Over-the-Counter Human Use (the "TFM") to include professional labeling for dosing of sodium phosphates oral solution was filed on behalf of the C.B. Fleet Company. This Citizens Petition requests labeling to allow double dose administration of their sodium phosphate solution for bowel cleansing prior to gastrointestinal diagnostic examination.

The Fleet Petition includes two new studies as well as historical literature and adverse experience reviews which purport to be responsive to questions posed by FDA at a meeting held June 19, 2002. However, as discussed further below, careful examination of these reports verifies previous conclusions that the administration of double dose sodium phosphates oral solution is *not* safe, primarily due to dangerous electrolyte shifts. This problem, inherent in the use of saline hyperosmotic solutions, is exacerbated by the fact that the susceptibility of most patients, and particularly the elderly, to electrolyte changes is not adequately evaluated prior to administration of bowel preparation agents, in spite of labeling. This has been demonstrated in clinical studies and by the numerous, continuing, adverse reports published in the literature which the Fleet Petition dismisses as "very rare" and usually due to maladministration in "at risk" patients. Unfortunately, as these reports demonstrate, due to the OTC status of oral phosphates solutions, a presumption of safety exists among consumers and practioners which makes maladministration a likely event.

Fleet PS9902 Study (Fleet Exhibit A)

This unpublished clinical trial of 225 patients compared two double dose Phosphosoda® bowel cleansing regimens (denoted as "2X30ml" or "2X45ml") to a polyethylene glycol lavage (GoLYTELY®). In both Phosphosoda treatment groups, the doses of sodium phosphates solution were administered about 12 hours apart. Blood samples were taken for analysis at baseline (before preparation), after preparation prior to colonoscopy and 24 hours later (follow-up). Patients with a history of heart or renal failure and patients with electrolyte disturbances were excluded. Enrolled patients were also evaluated by 12 lead electrocardiogram and excluded if the results were abnormal.

Although the study report notes relatively few instances of reportable out-of-range serum electrolytes following Phosphosoda preparation, inspection of the Investigational Plan section reveals that some electrolytes relevant to an assessment of

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60 Columbian Street West, P.O. Box 850929, Braintree, MA 02185-0929 • www.braintreelabs.com • (781) 843-2202 • FAX (781) 843-7932 • 1-800-874-6756

safety were given much wider, and therefore forgiving, reportable range definitions (see page 34 of PS9902 report). This is shown below in Table A:

Table A
Comparison of Electrolyte Values

Electrolyte	Not Reportable PS-9902	Normal Reference (1)
Calcium mg/dl	8.0 – 10.6	8.5 – 10.5
Phosphorus mg/dl	2.0 – 8.6	2.6 - 4.5
Sodium mEq/l	135 - 152	135 - 145

This definition of reportable out-of-range values has the effect of artificially reducing the number of out-of-range values that must be reported, essentially increasing the "false negative" rate. Thus the adverse experience data presented in Table 9 (page 54) of the PS9902 study report cannot be assessed and is presumably much greater than shown. It is useful to compare the results for the 2X45ml dose of the PS9902 study with the Fleet F00.02 study (see page 33 in Exhibit B in the Fleet Citizens Petition) which utilized more typical normal electrolyte ranges.

Table B
Comparison of Incidence of Out-of-Range Experience
Fleet PS-9902 vs. Fleet F00.20

Electrolyte	% of Study Patients PS-9902	F00.02
Hypocalcemia	0%	29%
Hyperphosphatemia	14.9%	100%
Hypernatremia	Not Reported	17%

Table B shows large differences between the studies with respect to reportable out-of-range electrolyte results, demonstrating the value to the Company of redefining the reportable range for relevant analytes.

Consistent with experience reported in the literature, serum potassium levels decreased significantly (0.49 and 0.44 mEq) for the 2X45ml and 2X30ml preparations respectively (page 62 of PS-9902 report). 20% of patients receiving the 2X30ml dose (versus 27% of 2X45ml patients) were noted in the report as having below normal serum potassium levels after preparation (page 69 of PS-9902 report). Hypokalemia was much more prevalent in female patients where as many as 43% of female patients that received the 2X30ml Phosphosoda preparation had below normal range serum potassium post

preparation (versus 28% of the 2X45ml female recipients – see page 70 of PS9902 report). These results indicate that there is little or no dose effect on this important electrolyte and suggest that the 2X30ml dose provides no improvement in safety. But, of greater concern, the report further observes that persistent hypokalemia occurred in 10% of Phosphosoda prepared patients (see page 69 of PS9902 report). This was observed at the follow-up measurement 24 hours after preparation and extends the previous findings of DiPalma et al (2). Clearly, persistent hypokalemia presents a significant risk to patients and further analysis is required, particularly for female patients.

Fleet F00.02 Study (Fleet Exhibit B)

This unpublished, open label study was performed in 24 healthy adults. The study was intended to evaluate the time course of the Fleet Phosphosoda 2X45ml double dose bowel preparation primarily on serum electrolytes out to 72 hours following completion of the second sodium phosphates dose. As in the PS9902 study, study subjects with a history of heart or renal failure and patients with electrolyte disturbances were excluded. Enrolled patients were also evaluated by 12 lead electrocardiogram.

As expected, nearly all study subjects experienced hyperphosphatemia. However, 29% (7 of 24) also experienced at least one episode of hypocalcemia. Of significant concern, following the final sodium phosphates dose, a number of study subjects show progressively higher serum calcium levels: as much as 0.5 mg/dl above baseline at the final 72 hour measurement (see figure 4, page 35, F00.20 study). This progressive effect requires further investigation, and may represent mobilization of calcium from hard tissue stores. This is suggested by a progressive increase in alkaline phosphatase levels (see Table 3, page 36, F00.20 Study). DiPalma et al (2) observed increases in serum PTH following sodium phosphate bowel preparation. Since PTH mediates bone remodeling an increase in alkaline phosphatase would be expected according to this mechanism.

Although the study report states that there "were no instances of clinically significant or symptomatic hypocalcemia", this is not particularly reassuring since all of the study subjects were healthy individuals very carefully prescreened including a 12 lead EKG. Never-the-less, 18 study subjects showed abnormalities in their post preparation EKG with an increase in QTc interval. This increase was correlated with the change in serum calcium and potassium levels (see pages 39-41, F00.20 Study).

Summary and Benefit-Risk Section (Fleet Exhibits H and M)

In the Summary section (Exhibit H) of the Citizens Petition, Fleet observes, following a review of all adverse experience, that 93% of reported ADRs are derived from clinical studies (see page 34, Exhibit H). This should not be viewed as reassuring since most clinical studies, such as those discussed above, carefully evaluate and eliminate study candidates with likely contraindications. Elsewhere, Fleet states that most of the adverse events reported in the literature represent incorrect administration or use in patients with contraindications, implying that this experience is somehow not relevant since the product is labeled against these uses (see Exhibit M Benefit-Risk, page 12). This is precisely the problem, where, due to its OTC status, there exists a perception of safety such that many practitioners are clearly unaware of the contraindications.

Discussion

The most obvious electrolyte abnormality induced by sodium phosphate bowel preparation is severe hyperphosphatemia as shown in all studies of this agent. Desmeules et al. (4) performed a renal biopsy on an elderly female patient that reported a malaise and developed chronic renal failure after sodium phosphate preparation. The biopsy revealed that the patient had developed nephrocalcinosis, although the patient had no risk factors for this condition. The authors concluded that the phosphosoda ingestion led to obstructive calcium phosphate crystalluria followed by intratubular nephrocalcinosis. Based on this observation, Desmeules et al suggest that high phosphate loads from phosphate based cathartics could induce calcium phosphate crystalluria resulting in long term renal damage in many more patients than are reported in the literature. As discussed further below, patients with any renal impairment (such as the elderly) that are not properly evaluated are clearly at greater risk.

The problem of physician maladministration was first reported by Chan and coworkers (3) who surveyed Canadian gastroenterologists. The survey revealed that more than 55% of those using the Phosphosoda preparation reported that they did not exclude its use in patients with renal failure and 70% reported that they did not exclude its use in patients with cardiovascular disease. The authors concluded that "...a significant number of colonoscopists are not fully aware of its major complications.".

In a recent publication, Beloosesky et al (5), reported that more than half of 36 elderly hospitalized patients experienced hypocalcemia and hypokalemia following double dose oral sodium phosphate bowel preparation. In this study, the magnitude of the change in serum phosphorus resulting from the preparation was negatively correlated with creatinine clearance, thus patients with poorer clearance tended to experience greater hyperphosphatemia. Since renal function declines with age, elderly patients would be expected to be particularly susceptible. Beloosesky et al conclude that although the effects of Phosphosoda preparation on calcium and phosphorus were predictable, the magnitude and number of patients experiencing hypokalemia was not. The authors suggest that their study supports the idea, originally proposed by Hill et al (6), that some patients are in a state of relative potassium depletion which cannot be predicted by serum potassium measurement.

Beloosesky et al further showed that oral sodium phosphate ingestion resulted in marked urinary phosphate excretion without changing urinary sodium excretion. These investigators thus explain that the severity of hypokalemia observed in their elderly patients was most likely due to a combined effect of intestinal losses of potassium (due to diarrhea) and an impaired ability of some patients to conserve potassium due to age related renal decline. The consequences of these potassium losses, of course, would be greatly exacerbated by any pre-existing state of potassium depletion.

Chan et al (3) note correctly that, unlike routine practice, most published studies of Phosphosoda assiduously evaluate and exclude patients with labeled contraindications. The same is true for the Fleet studies PS9902 and F00.02 discussed above. Indeed, these latter studies add a further exclusion through use of 12 lead EKG (two patients were in fact excluded from the PS9902 study due to EKG abnormalities). Unfortunately, as clearly demonstrated by Chan, actual practice rarely includes an adequate evaluation for contraindications and most certainly do not include an EKG. Beloosesky et al (5) show

that the elderly, probably due to a silent decline in renal function, are susceptible to hypokalemia of unpredictable severity.

The problems of both unpredictable effects in the elderly and maladministration are likely to continue to be refractory to changes made to the Fleet Phosphosoda labeling (since this requires that practioners be aware of labeling in the first place). Of particular concern is that even using a reduced dose, as in the 2X30ml preparation reported in Fleet study 9902, does not ameliorate the incidence of hypokalema in female patients. In the context of the market withdrawal of Propulsid (an agent with potassium channel blocking activity), which caused serious heart arrhythmias, including ventricular fibrillation, ventricular arrhythmias, torsades de pointe, QT prolongation, cardiac arrest and sudden death, the effect of Phosphosoda on potassium is alarming. Since the marketing of the Phosphosoda double dose regimen has continued unabated with new kits being devised (7), additional adverse events of increasing severity can be expected.

In conclusion, due to unresolved safety problems (particularly nephrocalcinosis and unpredictable hypokalemia) which have been demonstrated to be unresponsive to labeling, the Fleet Citizens Petition requesting labeling for their double dose bowel preparation regimen should be denied.

Sincerely,

Mark vB. Cleveland, Ph.D.
Vice President
Regulatory and Scientific Affairs

References (attached)

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2. DiPalma JA, Buckley SE, Warner BA, Culpepper RM: Biochemical effects of oral sodium phosphate. Digestive Dis and Sci 1996;41:749-753.

3. Chan A, Depew W, Vanner, S: Use of oral sodium phosphate colonic lavage solution by Canadian colonoscopists: pitfalls and complications. Can J Gastro. 1997;11:334-338.

4. Desmeules S, Bergeron MJ, Isenring P: Acute phosphate nephropathy and renal failure. NEJM 2003;349:1006-1007.

5. Beloosesky Y, Grinblat J, Weiss A, et al.: Electrolyte disorders following oral sodium phosphate administration for bowel cleansing in elderly patients. Arch Intern Med 2003;163:803-808.

6. Hill AG, Teo W, Still A, et al.: Cellular potassium depletion predispose to hypokalemia after oral sodium phosphate. Aust N Z J Surg 1998;68:856-858.

7. Fleet Phosposoda ACCU-PREP brochure.