

The other clinical study (Ref. 7) was a 21-day, double-blind, randomized, placebo-controlled clinical study comparing two dose levels of bismuth subsalicylate in the prevention of travelers' diarrhea. Subjects were randomly assigned bismuth subsalicylate either 1.05 g per day (262.5 mg four times a day) (low dose), 2.1 g per day (525 mg four times a day) (high dose), or 7.15 g lactose (two placebo tablets four times a day). Additional analyses were also done. In the original analysis, the difference in diarrheal incidence rate from placebo was only statistically significant for the high-dose regimen. Supplemental comparisons done only for subjects who completed all 21 days of the study or who contracted diarrhea ("four or more unformed stools in a 24-hour period") were consistent with the primary efficacy comparisons. The investigators concluded that 525 mg bismuth subsalicylate four times a day provides a statistically significant reduction in the occurrence of diarrhea for up to 3 weeks and that 262.5 mg four times a day provides a marginal benefit that could be considered in the range of the minimum effective dose. However, this significant reduction in the incidence of diarrhea was not discernible when the data from both analyses were evaluated. Similarly, when the effects of the "high" and "low" bismuth subsalicylate dose were compared, no significant difference in the incidence of diarrhea was detected.

Only the second clinical study (Ref. 7) showed that bismuth subsalicylate tablets in a dosage of 525 mg four times a day may be effective in the prevention of travelers' diarrhea. However, an additional double-blind, randomized, placebo-controlled study by another independent investigator is needed to substantiate the study findings. The agency's detailed comments and evaluation of the data are on file in the Dockets Management Branch (Ref. 8).

The agency is concerned about the benefit-to-risk ratio associated with prophylactic use for several weeks for acute diarrhea, which itself is usually self-limiting, lasting only from 24 to 72 hours. Although there have been no reported cases of bismuth encephalopathy associated with the dosage and time period usually recommended for OTC use, the safety of prophylactic use for 3 weeks to persons traveling to high-risk diarrhea areas is not well documented. Thus, any future study of effectiveness should also include an evaluation of tinnitus and other subtle and mild central nervous system symptomatology, such as vertigo, gait disturbances, etc. An

evaluation of bismuth pharmacokinetics during the period of use would also be desirable.

(Comment 3) One comment submitted four clinical studies (Refs. 9 through 14) to support the use of bismuth subsalicylate for the treatment of diarrhea for the three labeling indications discussed in the proposal (51 FR 16138 at 16140 to 16141). The comment also requested that a travelers' diarrhea claim for bismuth subsalicylate be included in the final monograph.

The agency has determined that these studies (DuPont, Steffen-DuPont, Steffen, and Gryboski) support the use of bismuth subsalicylate to treat the symptoms of acute nonspecific diarrhea and, tentatively, travelers' diarrhea. The DuPont and Steffen-DuPont studies were double-blind, randomized, parallel group trials comparing the efficacy of bismuth subsalicylate with placebo for the treatment of acute, nonspecific diarrhea. The DuPont study (Ref. 10) involved 112 students from the United States enrolled at universities in Mexico and who were suffering from diarrhea. The subjects received placebo or bismuth subsalicylate at a dose of 525 mg per 30 milliliter (mL) solution every half hour up to a maximum of eight doses (4.2 g) per day for 2 days. The students were given diary cards on which to record the time of passage of each stool, the stool consistency, the severity of any associated symptoms, and the times and amounts of medication ingested. Diary cards were maintained for 72 hours (the 48-hour treatment period and the ensuing 24 hours). Diarrhea was defined as one or more symptoms of enteric infection (e.g., fever, abdominal discomfort, urgency, nausea) plus either three or more unformed stools in an 8-hour period or four or more such stools in a 24-hour period.

The primary effectiveness measures were reduction in the duration of diarrhea, improvement in stool consistency, and reduction of stool frequency. Results significantly favoring bismuth subsalicylate were obtained for all parameters of effectiveness. Half of the subjects who took bismuth subsalicylate experienced total relief by 27 hours. Additionally, 78 percent of the subjects treated with bismuth subsalicylate had total relief of diarrhea and all associated symptoms at the end of the 72-hour period compared with 50 percent of the placebo-treated subjects. The mean percentage of total firm stools among subjects treated with bismuth subsalicylate was numerically greater than for the placebo-treated subjects at all time intervals, and significantly greater for the first 24 hours after

treatment (36.6 percent versus 8.6 percent, $p < 0.01$). Stool frequency data also showed that the number of unformed stools was numerically lower for all time intervals after the first 12 hours for the bismuth subsalicylate subjects compared to the placebo subjects. However, only the 12- to 24-hour interval showed statistical significance ($p = 0.04$). Subjects global assessment of relief was 92 percent for those who received bismuth subsalicylate compared to 73 percent for those who received placebo on day 1 ($p = 0.032$) and 98 percent versus 86 percent on day 2 ($p = 0.059$). The physician's global ratings showed relief in 84 percent of subjects treated with bismuth subsalicylate and 58 percent of placebo subjects ($p < 0.01$).

The Steffen-DuPont study (Ref. 10) included 130 Swiss nationals traveling in West Africa. It had essentially the same design as the DuPont study except that diarrhea was defined as one or more watery stools (pourable) or one or more pasty stools (do not retain shape). Subjects were given bismuth subsalicylate 1.05 g every hour up to a maximum of four doses (4.2 g) per day for 2 days, or placebo. Results indicated that 69 percent of subjects treated with bismuth subsalicylate had relief after 48 hours compared to 40.6 percent for placebo subjects. Stool consistency was numerically higher for subjects treated with bismuth subsalicylate than subjects who received placebo. Subject's global assessments of relief was 76 percent for those who received bismuth subsalicylate and 72 percent for those who received placebo on day 1 ($p = 0.76$). On day 2, a significantly greater percentage of subjects treated with bismuth subsalicylate reported relief (89 percent) compared to placebo subjects (73 percent), $p = 0.02$.

A subgroup analysis on subjects identified as having entry criteria (three or more unformed stools before entry) similar to subjects in the Dupont study allowed for direct comparisons of these two studies. The analysis confirmed a significant effect for bismuth subsalicylate over placebo.

The Gryboski study (Refs. 9 and 10) was a double-blind, placebo-controlled, parallel clinical trial, conducted for 7 days, that involved 29 infants and children (age range 2 to 70 months) with chronic diarrhea, defined as a change in the consistency of the stool to watery or soft (mushy) and of greater than 2 weeks duration. A bismuth subsalicylate suspension containing 525 mg/30 mL was given based on age as follows: 6 weeks to 2 years, 2.5 mL; 2 to 6 years, 10 mL. The results indicated that bismuth subsalicylate significantly