



DEPARTMENT OF HEALTH & HUMAN SERVICES

HFA-305
Public Health Service

Food and Drug Administration
Rockville MD 20857

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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

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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:

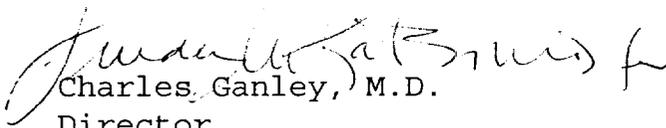
1. The results of the carcinogenicity study with bisacodyl in heterozygous p53 transgenic mice are acceptable.
2. Bisacodyl at oral doses up to 8000 mg/kg/day was not found to be tumorigenic in heterozygous p53 transgenic mice.
3. Based on currently available information, no further carcinogenicity testing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

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,



Charles Ganley, M.D.

Director

Division of OTC Drug Products

Office of Drug Evaluation V

Center for Drug Evaluation and Research