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D-55216 Ingelheim

CLINICAL TRIAL REPORT

Doc. No.:

U98-0150

BI Trial No.: 122.51 (ASM 93/1)

Test Substance(s): Bisacodyl, 4,4'-diacetoxy-diphenyl-(pyridy-2)-methane (-bisacodyl),
Dulcolax®

Title: Comparative Safety and Efficacy of Bisacodyl Sugar-coated Tablets in
the Treatment of Constipation

Clinical Phase: IV

GCP Compliance: yes

Author(s): Dr. Jean-Michel Vix, Tel No. 0049/6132/778296,
Fax 0049/6132/773818,
Kathrin Krakauer, Vaughan Reed

Principal/Coord.

Investigator: Susanne Kienzle-Horn

Institute/ Euro Bio-Pharm, Clinical Services, Koenigsteiner Str. 10

Department(s): 65812 Bad Soden, Germany

Date of Report: July 30, 1997

Dates of Trial: from May 14, 1994 to August 15, 1994

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3. SYNOPSIS AND TRIAL ABSTRACT

3.1 SYNOPSIS

Name of company: Boehringer Ingelheim		Tabulated Study Report		(For National Authority Use only)
Name of finished product: Bisacodyl		Page:	Number:	
Name of active ingredient: 4,4'-diacetoxy-diphenyl-(pyridyl-2)-methane (-bisacodyl)				
Ref. to Documentation:	Volume:	Page: to	Addendum No.:	
Report date: July 30, 1997	Number:	Study period (years): 1 5/94-8/94		
Title of study:	Comparative Safety and Efficacy of Bisacodyl Sugar-coated Tablets in the Treatment of Constipation			
Investigator:	Dr. med. von Behren, Dr. med. S. Berger, Dr. med. Degel, Dr. med. Herrmann, Dr. med. K.-D. Herzog, Dr. med. Mulverstedt, Dr. med. Najman, Dr. med. H.-J. Reimann, Dr. med. L. Schinke and Dr. med. U. Walther			
Study centre(s):	Wiesbaden, Wiesbaden, Offenbach, Frankfurt, Wiesbaden, Giessen, Frankfurt, Wiesbaden, Giessen and Wiesbaden			
Publication (reference):	None			
Clinical phase:	Phase IV			
Objective:	To assess the safety and efficacy of Bisacodyl sugar-coated tablets versus placebo in the treatment of constipation.			
Methodology:	Following a three day run-in period, patients were randomly assigned to receive either bisacodyl 5 mg sugar-coated tablets, to be taken at a dose of 10 mg once daily immediately prior to bedtime for three days, or matching placebo tablets to be taken once daily immediately prior to bedtime for three days. Patients recorded the frequency and consistency of bowel movements in daily diaries to assess the effectiveness of bisacodyl on a daily basis. The safety of bisacodyl was evaluated through the assessment of adverse events and by monitoring any clinically significant changes in laboratory values or physical examination findings. The investigator performed a global assessment of efficacy and of tolerance through patient questioning.			
No. of subjects entered:	55 patients entered (28 bisacodyl, 27 placebo)			
total:	54 patients treated			
each treatment:	27 patients bisacodyl; 27 patients placebo			
Diagnosis and main criteria for inclusion:	Patients diagnosed with constipation, defined as acute and habitual constipation and who met other entrance criteria.			
Test product:	bisacodyl			
dose:	5 mg sugar-coated tablets			
mode of admin.:	taken orally once daily immediately prior to bedtime for three days at a dose of 10 mg/day			
batch no.:	30902			
Duration of treatment:	3 days.			

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Reference therapy:				
dose:		placebo tablets		
mode of admin.:		taken orally once per day immediately prior to bedtime for 3 days		
batch no.:		30703		
Criteria for evaluation:				
Efficacy:		The criteria for efficacy were based on the evaluation of the primary efficacy variables, frequency of bowel movements and stool consistency compared to baseline. Patients were to record in daily diaries the number of bowel movements per day and the consistency of stools, for which days 0, 1 and 2 were the baseline period and days 2, 3 and 4 were the treatment period. For each bowel movement patients rated the consistency of their stools as either liquid, soft, well formed or hard. In addition, the investigator performed a global assessment of efficacy which was used as a secondary efficacy assessment. Each investigator provided a 4-step evaluation of severity of constipation by rating the frequency of bowel movements and consistency of stools on Study Day 5 in comparison to Study Day 2 using the following scale: worsened = worsening of either number of bowel movements or consistency of stools while the other either worsened or remained unchanged; unchanged = number of bowel movements and consistency of stools remained unchanged; somewhat improved = improvement of either number of bowel movements or consistency of stools while the other remained unchanged; significantly improved = improvement in both number of bowel movements and consistency of stools.		
Safety:		Patients were to record daily the occurrence of any adverse events in their diary. In addition to these events, any adverse events elicited in questioning by the investigator were recorded in the case report form. The investigator was to assess and record any adverse event in detail on the adverse events case report form including: the date and time of onset, description, severity, duration and outcome, etiology, relationship of the adverse event to the study drug, and action taken. The severity of adverse events was graded as mild, moderate or severe. The relationship of the adverse event to the study drug was assessed as concurrent condition, remote, possible, probable or definite. Laboratory tests were performed at baseline (Visit 2) and end of treatment (Visit 3) and all laboratory values considered clinically significantly abnormal by the investigator were recorded.		

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Statistical methods:				
<p>Sample Size Under the assumption that at least 80% of the patients treated with bisacodyl will show improvement of their constipation symptoms, a sample size of 22 (28) patients per treatment arm will provide 80% power to detect a treatment difference of 40% (35%) vs placebo with a two-sided test at the 0.05 level of significance.</p>				
<p>Efficacy Variables Primary Efficacy Variables <u>Number of Bowel Movements</u> - The total number of bowel movements per day was calculated for each patient. The average daily number of stools over the treatment period was calculated; <u>Consistency of Stools</u> - Patients were asked to record the consistency of each stool as being liquid, soft, well formed, moderately hard, or hard on the patient diary. The following scores were used: liquid = 1, soft = 2, well formed = 3, moderately hard = 4, and hard = 5. The amount of stools of each type was calculated for each patient. A daily stool consistency score was obtained by multiplying the number of stools of each consistency class by the appropriate score and dividing by the total number of stools that day. Stool consistency scores for the baseline treatment periods were computed by the analogous calculation. Changes from baseline to treatment in the daily number of stools and in stool consistency score were analyzed with ANOVA. The poolability of the by-center results was tested with the F-test for the interaction term from an ANOVA model with treatment, center, and treatment by center interaction effects at the 0.10 level of significance. If the interaction effect was not significant it was dropped from the model and the two-way main effects model was used to make treatment comparisons.</p>				
<p>Secondary Efficacy Variables <u>Investigator's Global Assessment of Efficacy</u> - The 4-step evaluation of severity of constipation (worsened, unchanged, somewhat improved, significantly improved) provided by the investigator was used as a secondary efficacy assessment; <u>Number of Bowel Movements and Consistency of Stools</u> - The number of bowel movements and the average of stool consistencies was summarized by treatment group for each study day with descriptive statistics including the mean, median, standard deviation and range. The investigator's global assessment of efficacy was analyzed with a Mann Whitney test.</p>				
<p>Safety Safety was analyzed throughout the course of this study by monitoring the occurrence of adverse events and changes in laboratory variables (including serum electrolyte levels). All patients who took at least one tablet were eligible for safety data analysis. The incidence of adverse events was summarized by treatment group with patient counts and percents. The number of patients reporting clinically significant shifts in serum electrolytes and other laboratory parameters was summarized by treatment group. Statistical treatment comparisons for adverse events and changes in laboratory variables were made using Fisher's exact test.</p>				

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Report date: July 30, 1997	Number:	Study Period (years): 1 5/94-8/94		
SUMMARY - CONCLUSIONS:				
<p>Efficacy results: The primary efficacy analysis for mean stool number and consistency over the three day study period indicated the value for mean stool count for the bisacodyl treatment group (median = 1.5) was statistically significantly ($p = 0.003$) greater than that for the placebo group (median = 0.8). Stool consistency was also improved in favor of the active treatment. The median stool consistency value was 2.4 on bisacodyl and 4.5 on placebo ($p = 0.001$ using the CMH test stratified for baseline consistency). Analysis of the secondary efficacy variables indicated there was a significant difference in global efficacy ($p = 0.045$) with median values of 1.0 (significant improvement) for the bisacodyl treatment group and 2.5 (value between somewhat improved and unchanged) for the placebo group.</p>				
<p>Safety results: Of the 27 bisacodyl treated patients who were eligible for the safety analysis, 15 (55.6%) reported a total of 37 adverse events. By comparison 18 (66.7%) of the placebo patients reported a total of 29 adverse events. The most frequently reported adverse events actually representing laboratory abnormalities (10/26, 38.5%, bisacodyl; 11/25, 44.0%, placebo) were white cell and reticuloendothelial system disorders (mild leukocytosis). Other frequently reported adverse events were gastro-intestinal (4/26, 15.4%, bisacodyl; 5/25, 20%, placebo), metabolic and nutritional (3/26, 11.5%, bisacodyl; 2/25, 8.0%, placebo), urinary system disorders (3/26, 11.5%, bisacodyl; 1/25, 4.0%, placebo) and liver and biliary system disorders (1/26, 3.8%, bisacodyl; 2/25, 8.0%, placebo). All of the adverse events reported on bisacodyl were rated mild in intensity; two events reported on placebo were rated as moderate ($p = 0.107$) and the remainder as mild. No patient deaths occurred, and no adverse events occurred which were serious, severe or resulted in discontinuation of the study drug. All of the adverse events could be easily tolerated and were clinically not relevant. There was no significant difference between the treatment groups with regard to the global tolerance score. Few clinically relevant laboratory observations were noted and no clinically significant differences were noted between treatment groups. With the assessment of patients' vital signs there was no evidence of untoward effects caused by bisacodyl.</p>				
<p>Conclusions: In this double blind, multicenter, parallel comparison between two groups of 27 patients randomly assigned to receive either bisacodyl or placebo, bisacodyl was significantly better than the placebo in relieving constipation. The value for mean stool count for the bisacodyl treatment group (median count = 1.5) was statistically significantly ($p = 0.003$) greater than that for the placebo group (median count = 0.8). Stool consistency was also improved in favor of the active treatment. The median stool consistency value was 2.4 on Bisacodyl and 4.5 on placebo ($p = 0.001$ using the CMH test stratified for baseline consistency). The patients on bisacodyl reported more adverse events (37) compared to placebo (29). However, no particular pattern of side effects emerged as being more likely to occur on the active treatment compared to placebo.</p>				