SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development
Name of Finished Product	VERMOX®
Name of Active Ingredient	Mebendazole

Protocol No.: MEBENDAZOLGAI3002

Title of Study: An Open-Label, Single-Dose Study to Assess the Safety of 500-mg Mebendazole Chewable Formulation in Children 2 to 10 Years of age, Inclusive

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Publication (Reference): None

Study Period: 24 February 2010 to 12 March 2010; database lock date: 25 May 2010

Phase of Development: 3

Objective: The primary objective of this study was to assess the safety and tolerability of mebendazole 500-mg chewable tablet formulation in a pediatric population (children 2 to 10 years of age, inclusive).

Methods: This was an open-label, single-center, single-dose, single-arm safety study. This study consisted of a screening visit on Day 1 when all study related screening procedures were performed. Eligible children were entered into the open-label phase of the study and administered a single mebendazole 500-mg chewable tablet on Day 1. The children remained at the study center and adverse events were recorded approximately 30-minutes postdose. Subjects returned to the study center 3 days (±1 day) after the single-dose administration on Day 1 and adverse events were recorded again. Adverse events were assessed by direct observation of the subject by the investigator, or reported by the parent (or guardian), or both.

Number of Subjects (planned and analyzed): Planned: approximately 375 subjects (with at least 120 subjects under 6 years of age) were planned to be enrolled in this study to ensure that 300 subjects would complete the study.

Analyzed: Three hundred and ninety-six subjects were enrolled in this study (with 271 subjects under 6 years of age), of which 390 subjects (98%) completed the study. All subjects received a single oral dose of mebendazole 500 mg and were included in the safety analyses.

Diagnosis and Main Criteria for Inclusion: Otherwise healthy boys and girls, between 2 and 10 years of age, inclusive, from a high prevalence area where parasite infection was endemic, and who were able to chew the mebendazole chewable tablet, were enrolled in this study.

Test Product, Dose and Mode of Administration, Batch No.: Mebendazole 500-mg chewable tablets (Batch No.: 362061; Expiration Date: 31 October 2010) were provided as white, round-shaped tablets with a breaking line on 1 side and plain on the other side. On Day 1, a single mebendazole 500 mg tablet was chewed and swallowed by each subject. If desired, subjects were allowed to drink water when administered study drug.

Reference Therapy, Dose and Mode of Administration, Batch No.: Not Applicable.

Duration of Treatment: Subjects received a single-dose of mebendazole 500-mg chewable tablet, followed by a 3-day (±1 day) postdose safety assessment period.

Criteria for Evaluation:

Safety evaluations: Safety evaluations were based on adverse events, vital signs (axillary temperature, pulse, respiratory rate, and blood pressure [BP]) and a physical examination. Safety evaluations were performed on Day 1 (30 minutes postdose) and 3 days (±1 day) after study drug administration. Height and body weight were recorded at screening visit (Day 1).

Statistical Methods: Descriptive statistics were provided for the safety analysis set, defined as all subjects who received single-dose of mebendazole 500-mg chewable tablet.

Sample Size Determination: Assuming a 20% dropout rate, 375 subjects were to be enrolled in this study to ensure that approximately 300 subjects would complete all study related activities and assessments. There was at least a 90% probability that adverse events with an underlying true incidence of 1% would be detected with a sample size of 300 mebendazole-treated subjects who would complete the study.

Safety Analysis: Safety was evaluated by examining the incidence, severity, relationship to study drug, incidence and severity of adverse events, and change from baseline to the end-of-study (EOS)/early withdrawal visit in physical examination and vital sign measurements. Safety data were analyzed and stratified by baseline egg counts (from baseline stool samples).

RESULTS:

Three hundred and ninety-six subjects were enrolled in this study, of which 390 subjects (98%) completed the study. Six subjects were withdrawn from the study due to noncompliance with the study drug. Baseline egg count evaluation to determine the type(s) and severity of baseline soil-transmitted helminth (STH) infections was conducted in 352 subjects. Of these, 195 subjects reported a baseline STH infection: 181 subjects (45.7%) had light infections and 14 subjects (3.5%) had moderate infections; no subjects reported a severe infection. Baseline egg count was higher for trichuris infection (181 subjects) compared with hookworm (57 subjects) and ascaris infection (24 subjects).

SAFETY RESULTS:

There were no deaths, serious adverse events, or discontinuations due to adverse events reported in this study. Forty-four (11%) of 396 subjects reported at least 1 adverse event; the most commonly reported (ie, reported in ≥5 subjects) adverse events were pyrexia, diarrhea, lymphadenopathy, and cough. There was no specific correlation observed between baseline type and/or severity of helminth infection and frequency of adverse events. The number of subjects with adverse events was similar for subjects with light helminth infection at baseline (23 [13%] of 181 subjects) and subjects without helminth infection at baseline (18 [11%] of 157 subjects). In addition, with the exception of diarrhea, the frequency of adverse events was similar between the 2 age group strata: adverse events were reported in 31 subjects (11%) 2 to 5 years old and in 13 subjects (10%) 6 to 10 years old. Diarrhea was reported in 10 subjects (4%) 2 to 5 years old and no subjects 6 to 10 years old.

Most of the treatment-emergent adverse events (TEAEs) were mild to moderate in intensity. One severe adverse event (epistaxis) was reported in this study that was considered as not related to mebendazole by the investigator.

Most of the adverse events were considered doubtfully related to mebendazole administration. There was 1 TEAE (diarrhea) reported in this study that was considered moderate in intensity and probably related to mebendazole. None of the adverse events were considered very likely related to mebendazole by the investigator.

Two hundred and eighty-nine (73%) of 396 subjects reported vital sign values beyond clinically important limits. There was no specific correlation observed between baseline helminth infection and frequency of vital signs values beyond clinically important limits. Number of subjects with vital signs values beyond clinically important limits was similar for subjects with light helminth infection at baseline (133 [73%] of 181 subjects) and subjects without helminth infection at baseline (117 [75%] of 157 subjects). Twelve (86%) of 14 subjects with moderate helminth infection were noted with vital signs values beyond clinically important limits. Overall, 227 subjects (57%) had increased respiratory rate at baseline, compared with 249 subjects (63%) at end of study or early withdrawal.

Ninety-nine subjects were noted with abnormal physical examinations at screening; 72 of 98 subjects had normal physical examinations at the EOS visit (a single subject [100190] was not evaluated at EOS). A total of 47 subjects were noted with physical examination abnormalities at EOS in whom 24 abnormal physical examinations had been reported at screening for the same parameters. The percentage of subjects with abnormal physical examinations at EOS was similar in subjects without baseline helminth infection (17 [11%] of 157 subjects) and subjects with light helminth infection at baseline (26 [14%] of 181 subjects). There was no particular trend observed for shift in physical examination from screening to EOS visit for each parameter.

Abnormal physical examinations in 24 subjects were reported as adverse events in this study. The majority of these physical examination adverse events were reported in lymph node examination (8 subjects) and lung examination (6 subjects). Other physical examination adverse events reported were fever (4 subjects), abdominal distension (1 subject), diarrhea (1 subject), skin rashes (2 subjects), jaundice in eye (1 subject), oral pain (1 subject), and systolic murmur (1 subject).

Overall, there were no notable differences in the safety profile of new chewable formulation of mebendazole and the currently marketed VERMOX tablet.

STUDY LIMITATIONS: The lack of a placebo control in this study was noted as a study limitation by the Sponsor.

CONCLUSION:

Single-dose administration of mebendazole 500-mg chewable tablet is safe and well tolerated in children between 2 years and 10 years of age.