

1 SYNOPSIS

<p>Name of Sponsor/Company McNeil Consumer & Specialty Pharmaceuticals</p> <p>Name of Finished Product: Acetaminophen Extra Strength</p> <p>Name of Active Ingredient: Acetaminophen</p>	<p>Individual Study Table Referring to Part of the Dossier</p> <p>Volume:</p> <p>Page:</p>	<p>(For National Authority Use Only)</p>
<p>Title of Study: A Randomized, Double-Blind, Long-Term Comparative Study Evaluating the Safety and Efficacy of Acetaminophen (4000 mg/day) and Naproxen (750 mg/day) in the Treatment of Osteoarthritis of the Hip or Knee</p> <p>Investigators: Multiple (47 Investigators); see list of principal investigators in Appendix 14.1.4.</p> <p>Study Centers: Multiple (47 sites in United States [US]); see site addresses in list of principal investigators in Appendix 14.1.4.</p> <p>Publication (reference): Zinsenheim J, Benson G, Schweinle J, et al. Comparison of acetaminophen and naproxen for the management of mild-to-moderate osteoarthritis pain of the hip or knee. Presented at the 2nd Joint Scientific Meeting of the American Pain Society and the Canadian Pain Society. May 6, 2004. Vancouver, BC Canada.</p> <p>Study period: (date of first enrollment) May, 5, 2000 (date of last completed) June 6, 2003</p> <p>Phase of Development: III</p> <p>Objectives: To compare the relative long-term safety profile and efficacy of acetaminophen (4000 mg/day) and naproxen (750 mg/day) in the treatment of osteoarthritis of the hip or knee.</p> <p>Methodology: This study was a randomized, double-blind, single-dummy, active-controlled, outpatient, multi-dose, multicenter phase III study of approximately 560 subjects conducted at 47 sites in the United States (US). Two groups of subjects 40 to 75 years of age with mild to moderate pain secondary to osteoarthritis of the hip or knee were enrolled. For Group 1, approximately 480 subjects enrolled at 36 sites were to be treated for 12 months or until study discontinuation. For Group 2, approximately 80 subjects enrolled at 12 sites were to be treated for six months or until study discontinuation. In both groups, qualified subjects were to be randomly assigned in equal numbers to either acetaminophen 4000 mg/day or naproxen 750 mg/day and placebo after completion of the baseline visit. In order to be enrolled in the study, subjects must have reported a pain intensity over the 24 hours prior to</p>		

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enrollment of mild, moderate or moderately severe. Following an initial screening visit, a washout period, and determination of subject eligibility, laboratory evaluations, vital signs assessment, including subject respiration, pulse, blood pressure and weight, an alcohol consumption assessment, and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC OA Index) pain, stiffness and physical function subscales (visual analog scale [VAS]) score assessment were administered at baseline and at months 1, 3, 6, 9, and 12 or final visit for early discontinuation for Group 1 subjects and at baseline and months 1, 3, and 6 or final visit for early discontinuation for Group 2 subjects. Subjects were instructed to take a dose of study medication every four to six hours according to the specified dosing schedule. Subjects were to record in a diary all doses of study medication taken, the dates of all doses (per protocol), any symptoms of illness or discomfort, supplemental medications taken, or changes in the use of chronic medications throughout the course of the study until their final visit. No interim analyses were performed.

Number of Subjects (planned and analyzed): The study was designed for enrollment of approximately 560 subjects (480 subjects in Group 1 and 80 subjects in Group 2). A total of 581 subjects (476 Group 1, 105 Group 2; 290 acetaminophen, 291 naproxen) were randomized; 571 subjects (469 Group 1, 102 Group 2; 287 acetaminophen, 284 naproxen) were included in the safety analysis; and, 551 subjects (456 Group 1, 95 Group 2; 276 acetaminophen, 275 naproxen) were included in the modified intent-to-treat analysis.

Diagnosis and main criteria for Inclusion: Male or nonpregnant female age 40 to 75 with a history of OA for a minimum of six months characterized by mild to moderately severe pain that required the use of an analgesic agent on a regular basis for at least three months with a subjective positive response to this agent, with at least two of the following criteria: morning stiffness of <30 minutes duration, crepitus, bony tenderness, bony enlargement, and no palpable warmth, with radiographic evidence of grade 2 or 3 OA of the knee or hip within prior six months visit, was American College of Rheumatology (ACR) functional class 1 or class II, was able to walk at least 100 feet without an assistive device, had laboratory values consistent with a diagnosis of OA and had normal values for hemoglobin, hematocrit, creatinine, total bilirubin, albumin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase. Following a washout period, subjects must have reported mild to moderately severe pain over the previous 24 hours and demonstrated a minimum increase in the Western Ontario and McMaster Universities (WOMAC) OA index pain subscale score of 20% relative to the screening score.

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<p>Test Product, Dose and Mode of Administration, Batch Number: Two 500-mg caplets of acetaminophen (Tylenol Extra Strength) taken orally every four to six hours, control number Z-4396.</p> <p>Duration of Treatment: Acetaminophen and naproxen subjects in Group 1 were treated for 12 months and acetaminophen and naproxen subjects in Group 2 were treated for 6 months. No post treatment follow-up was performed, unless required for safety.</p> <p>Reference Therapy, Dose and Mode of Administration, Batch Number: One naproxen 375 mg caplet taken orally every eight to 12 hours, control number Z-4397, one naproxen-placebo caplet taken orally with each naproxen caplet (1st and 3rd daily dose), and two naproxen-placebo caplets taken orally every eight to 12 hours (2nd and 4th daily dose), control number Z-4398.</p> <p>Criteria for Evaluation:</p> <p>Efficacy: Primary measure: Change from baseline in the WOMAC OA Index pain subscale score at month 6 or at the final visit at the time of subject discontinuation during the first six months after baseline.</p> <p>Secondary measures:</p> <ul style="list-style-type: none"> • Change from baseline in the WOMAC OA Index stiffness and physical function subscale score at month 6 or at the final visit at the time of subject discontinuation during the first six months after baseline. • Change from baseline in the WOMAC OA Index pain, stiffness and physical function subscale score at month 12 or at the final visit at the time of subject discontinuation after baseline in Group 1 (12-month study). • Change from baseline in the WOMAC OA Index pain, stiffness and physical function subscale score at all other time points. <p>Safety: Adverse events (AEs), including AEs over time, laboratory tests, vital signs, including respiration rate, pulse, blood pressure, and body weight were assessed throughout the course of the study.</p> <p>Statistical Methods: Comparability between treatment groups was assessed using a one-way analysis of variance (ANOVA) with treatment as a factor for continuous baseline variables and Chi-square test for categorical baseline variables. If the cell size was less than five, Fisher's exact test was used.</p>		

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Comparability between treatment groups at baseline for WOMAC OA Index subscale scores was assessed using a one-way ANOVA with treatment as a factor. Analysis of covariance (ANCOVA) was used to test for differences between treatments with respect to the change from baseline in WOMAC OA Index subscale score with treatment and investigator as factors and baseline scores as a covariate.

The frequency of AEs, serious AEs, and AEs leading to withdrawal from the study were compared between treatment groups with Fisher's exact test. An ANOVA with the treatment as a factor was used to test for differences in treatment group in changes from baseline during the study at various time periods in vital signs.

Efficacy Results: 69.2% of subjects were female and 84.1% were Caucasian. Mean age of all subjects was 59.3 years. The only statistically significant difference between the treatment groups in the demographic and baseline characteristics was in height at baseline, where the acetaminophen group was statistically significantly ($p=0.0207$) taller than the naproxen group, however, the difference was of no clinical significance.

The baseline pain score was statistically significantly ($p=0.0269$) higher in the naproxen group (62.5) than in the acetaminophen group (58.3); the difference was not considered to be clinically important. Acetaminophen 4000 mg/day and naproxen 750 mg/day were equally effective in relieving pain following six and 12 months of treatment. Acetaminophen 4000 mg/day and naproxen 750 mg/day were equally effective in relieving stiffness and improving physical function at all time points evaluated. No statistically significant differences between treatment groups were observed for either the primary or any of the secondary efficacy endpoints.

Mean Primary and Secondary Efficacy Endpoints

Mean Change from Baseline at 6 months	Acetaminophen	Naproxen	p-Value
Primary WOMAC Pain Subscale Score	-21.6	-21.9	0.8847
Secondary WOMAC Stiffness Subscale Score	-20.6	-21.0	0.8529
Secondary WOMAC Physical Function Subscale Score	-18.9	-20.1	0.5842

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Safety Results:

Overall, 72.7% of all study subjects (71.8% acetaminophen and 73.6% naproxen) reported AEs; the difference between treatment groups was not statistically significant. Overall, 40.8% of all study subjects (38.3% acetaminophen and 43.3% naproxen) had AEs considered drug-related (certain, probable/likely, possible, or unlikely); the difference between treatment groups was not statistically significant.

The most common AEs were in the body as a whole (mainly pain, abdominal pain, infection, and headache) reported by 47.5% of all study subjects (46.0% acetaminophen and 48.9% naproxen) and in the digestive system (mainly dyspepsia) reported by 36.8% of all study subjects (33.4% acetaminophen and 40.1% naproxen). Significantly more subjects in the acetaminophen group reported diarrhea (11.5% acetaminophen, 5.6% naproxen, $p=0.0162$) and hypertension (4.5% acetaminophen, 1.4% naproxen, $p=0.0458$). Significantly more subjects in the naproxen group reported constipation (4.2% acetaminophen, 12.7% naproxen, $p=0.0002$), gastroenteritis (0.0% acetaminophen, 2.5% naproxen, $p=0.0073$), peripheral edema (2.1% acetaminophen, 5.3% naproxen, $p=0.0473$), arthrosis (0.7% acetaminophen, 3.5% naproxen, $p=0.0206$), and leg cramps (1.0% acetaminophen and 3.9% naproxen, $p=0.0323$).

The proportion of subjects reporting AEs in both treatment groups appeared to decrease over the 12-month study.

No deaths were reported during the study. Serious AEs were reported for 3.0% of all study subjects (3.5%, for acetaminophen, 2.5%, for naproxen). The difference between treatment groups was not significant. All serious AEs, except for one (gastrointestinal hemorrhage) in the naproxen group, were considered not related to study drug.

Overall, 23.5% of study subjects (24.7% acetaminophen, 22.2% naproxen) had AEs leading to early discontinuation (most commonly abdominal pain, pain, dyspepsia, and nausea). There were no statistically significant differences between treatment groups.

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No potentially clinically important laboratory values were observed for AST ($\geq 3x$ ULN), ALT ($\geq 3x$ ULN) or creatinine (increasing from baseline and $>1.5x$ ULN) in either treatment group. Overall, potentially clinically important values for hemoglobin (decline of ≥ 2 g from baseline) were observed in four (1.4%) subjects in the acetaminophen group and in six (2.1%) subjects in the naproxen group. Post-baseline hemoglobin values were below the normal range for one subject in the acetaminophen group and for two subjects in the naproxen group.

Conclusions:

- There was no statistically significant difference between the acetaminophen 4000 mg/day and naproxen 750 mg/day groups in the primary endpoint of change from baseline in the WOMAC OA Index pain subscale score at month 6 of treatment. While there was a statistically significant ($p=0.0423$) difference between treatment groups in change from baseline in Black subjects, this difference was not considered to be clinically important.
- There were no statistically significant differences between the acetaminophen 4000 mg/day and naproxen 750 mg/day groups in the secondary endpoints of change from baseline in the WOMAC OA Index stiffness and physical function subscale scores at month 6 of treatment.
- There were no statistically significant differences between the acetaminophen 4000 mg/day and naproxen 750 mg/day groups in the secondary endpoints of change from baseline in the WOMAC OA Index pain, stiffness, or physical function subscale scores at months 1, 3, 9 or 12, or end of study.
- Acetaminophen 4000 mg/day and naproxen 750 mg/day were well tolerated and no important differences in safety were identified over six to 12 months of treatment. There was no statistically significant difference between treatment groups in the overall incidence of adverse events. The severity and nature of adverse events were similar for acetaminophen and naproxen. No deaths were reported. Other serious adverse events were reported for 3.0% of subjects, with no statistically significant difference between treatments.

Date of Report: June 20, 2005

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