

<p>Name of Sponsor/Company McNeil Consumer & Specialty Pharmaceuticals</p> <p>Name of Finished Product: Extra Strength Tylenol® (gel- dipped caplets)</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, Double-Dummy, Placebo-Controlled, Parallel Group Study of Acetaminophen 1000 mg and Ibuprofen 400 mg in Postoperative Dental Pain</p> <p>Investigator: Dennis N. Adamson, DDS</p> <p>Study Center: JBA Research Recovery Center 777 North 500 West, Suite 106 Provo, UT 84604</p> <p>Publication: None</p> <p>Study period: Date of first enrollment: December 5, 2003 Date of last completed: February 18, 2004</p> <p style="text-align: right;">Phase of Development: IV</p> <p>Objectives: The primary objective was to compare the efficacy and safety of single doses of acetaminophen and ibuprofen when administered to study subjects experiencing moderate to severe postoperative dental pain secondary to the surgical extraction of a minimum of three molars, with at least one being partial or complete bony mandibular third molar impaction.</p> <p>Methodology: This was a randomized, single-dose, double-blind, double-dummy, placebo-controlled, parallel group study. A total of 222 healthy subjects reporting moderate to severe pain following the surgical extraction of a minimum of three molars (with at least one partial or complete bony mandibular third molar impaction) were enrolled. Eligible subjects were randomly assigned with equal probability among three treatment groups: acetaminophen gel-dipped caplets and placebo ibuprofen liquid-filled gelatin capsules, placebo acetaminophen gel-dipped caplets and ibuprofen liquid-filled gelatin capsules, and placebo acetaminophen gel-dipped caplets and placebo ibuprofen liquid-filled gelatin capsules.</p> <p>Following the recording of baseline pain intensity and the administration of study medication, subjects evaluated their pain intensity and pain relief relative to baseline at various timepoints up to 4 hours after taking study medication. Pain intensity was assessed using a five-point scale consisting of none (0), mild (1), moderate (2), moderately severe (3), and severe (4). Pain relief from baseline was evaluated on a five-point scale consisting of none</p>		

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<p>(0), a little (1), some (2), a lot (3), and complete (4). At the end of the first hour of the observation period or at the time of taking supplemental analgesic medication, whichever occurred first, subjects made an overall (global) assessment of the study medication, based on a five-point scale consisting of poor (0), fair (1), good (2), very good (3), or excellent (4). Subjects were required to remain at the study site for the duration of the four-hour observation period whether they received rescue treatment or not.</p> <p>Number of Subjects (planned and analyzed): 216 planned (72 per treatment group), 222 analyzed (74 acetaminophen, 74 ibuprofen, 74 placebo).</p> <p>Diagnosis and Main Criteria for Inclusion: The main entry criteria were age ≥ 15 years, weight ≥ 100 pounds, body mass index of 18 to 28 (inclusive), and the presence of moderate to severe pain and a rating of at least 50 mm on a 100 mm visual analog scale (VAS) following the extraction of a minimum of three molars (including at least one partial or complete bony mandibular molar impaction).</p> <p>Test Product and Reference Therapy, Dose, Mode of Administration, and Control Number: Subjects were randomly assigned to receive a single oral dose of one of the following three treatments: acetaminophen 1000 mg, ibuprofen 400 mg, or placebo.</p> <p>Duration of Treatment: Subjects were treated with a single oral dose of study medication administered by mouth (two caplets and two capsules) after moderate to severe pain was reported following dental surgery. Subjects were monitored at the site by study staff for four hours after dosing.</p> <p>Criteria for Evaluation:</p> <p>Efficacy: Efficacy parameters included:</p> <ul style="list-style-type: none"> • Pain intensity differences from baseline and pain relief at each measurement time. • Area under the curve of the pain relief scores from zero to one hour (TOTPAR1). • Area under the curve of the pain intensity differences from baseline scores from zero to one hour (SPID1). • Subject's global assessment of medication pain relief at one hour. <p>Safety: Safety was assessed by monitoring adverse events occurring throughout the study.</p>		

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<p>Statistical Methods: The primary analysis was conducted on the intent-to-treat (ITT) population, which consisted of all subjects who took study medication. Comparisons of mean pain relief and mean pain intensity differences from baseline at each measurement interval were analyzed with two-sample t-tests. TOTPAR1 and SPID1 were compared with t-tests. The one-hour global rating was analyzed with a Cochran-Mantel-Haenszel test using modified ridits scores to test whether row mean scores differed. All comparisons were evaluated at a two-tailed alpha level of 0.05. The distribution of time to rescue and the proportion of subjects receiving rescue treatment were summarized with descriptive statistics. Safety was evaluated by encoding all verbatim adverse reactions to standard dictionary coding terms, and tabulating the overall safety profiles according to system organ class, severity, and relatedness to study treatment. Fisher's two-sided exact test was used to test treatment group differences in adverse event frequencies.</p> <p>Efficacy Results: The results for mean pain intensity differences from baseline indicated that statistical superiority to placebo was achieved beginning at 10 minutes post-dose in the acetaminophen group ($p = 0.042$) and 15 minutes post-dose in the ibuprofen group ($p = 0.002$), and this superiority was maintained at each subsequent timepoint.</p> <p>Mean TOTPAR1 and SPID1 values were significantly higher in both the acetaminophen ($p < 0.001$) and ibuprofen ($p < 0.001$) groups than in the placebo group. Relative to subjects in the placebo group, proportionately more of the subjects receiving acetaminophen and ibuprofen rated their overall impression of study medication for the first hour post-dose as "Excellent," "Very Good," or "Good." Statistical tests of differences between the active treatment arms and placebo were significant ($p < 0.001$).</p> <p>The median time to rescue was 125 minutes, 82.5 minutes, and 64 minutes for the acetaminophen, ibuprofen, and placebo arms, respectively. One subject in the placebo group required rescue treatment during the first 60 minutes after dosing. At the end of the 60- to 90-minute post-dose interval, 4.1%, 5.4%, and 58.1% of subjects in the acetaminophen, ibuprofen, and placebo groups, respectively, received rescue treatment. Corresponding percentages for the 3- to 4-hour interval were 20.3%, 10.8%, and 75.7%.</p>		

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<p>Safety Results: Overall, adverse events were reported by 23.0%, 28.4%, and 20.3% of subjects in the acetaminophen, ibuprofen, and placebo groups, respectively; the differences among treatment groups were not statistically significant. The most frequent adverse events were nausea (reported by 8.1%, 6.8%, and 1.4% of subjects in the acetaminophen, ibuprofen, and placebo groups, respectively) and headache (reported by 4.1%, 5.4%, and 6.8% of subjects in the acetaminophen, ibuprofen, and placebo groups, respectively). There were no statistically significant differences among treatment groups in adverse event frequencies. Drug-related adverse events were reported by 10.8%, 13.5%, and 9.5% of subjects in the acetaminophen, ibuprofen, and placebo groups, respectively; the differences among treatment groups were not statistically significant. One subject in the placebo group reported a serious adverse event, and one subject in the placebo group withdrew from the study due to adverse events.</p> <p>Conclusions:</p> <ul style="list-style-type: none"> • The mean pain intensity differences from baseline were statistically significantly superior to placebo beginning at 10 minutes post-dose in the acetaminophen group and 15 minutes post-dose in the ibuprofen group. • Both acetaminophen and ibuprofen were statistically significantly superior to placebo for the secondary endpoints TOTPAR1, SPID1, and global rating. • All study treatments were well tolerated and no safety issues were identified in this study. Overall, 23.9% of subjects reported adverse events; differences among treatment groups were not statistically significant. One serious adverse event and one withdrawal due to adverse events were reported, both in subjects from the placebo group. <p>Date of the Registry Synopsis: September 29, 2005</p>		

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