ORTHO-McNEIL PHARMACEUTICAL, INC.

CLINICAL STUDY REPORT

A COMPARISON OF THE EFFICACY AND SAFETY OF ULTRACET™ (TRAMADOL HCL/ACETAMINOPHEN) VERSUS ULTRAM® (TRAMADOL HCL) VERSUS PLACEBO IN SUBJECTS WITH PAIN FOLLOWING ORAL SURGERY (PROTOCOL CAPSS-241; PHASE 4)

PRINCIPAL INVESTIGATOR:	James R. Fricke, Jr., D.D.S., M.S.D.
DATE OF STUDY INITIATION	November 8, 2002
DATE OF STUDY COMPLETION	February 7, 2003

This trial was conducted in compliance with the Declaration of Helsinki as adopted by the 18th World Medical Assembly in Helsinki, Finland, in June 1964, amended by the 29th World Medical Assembly in Tokyo, Japan, in October 1975, the 35th World Medical Assembly in Venice, Italy, in October 1983, and the 41st World Medical Assembly in Hong Kong, China, in September 1989. The trial was also conducted in compliance with the International Committee on Harmonisation (ICH) Topic 6 Guideline for Good Clinical Practices, Step 5 (Consolidated Guidelines 1.5.96); "Note for Guidance on Good Clinical Practices" (CPMP/ICH/135/95, effective 17 January 1997).

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A Comparison of the Efficacy and Safety of ULTRACET™ (Tramadol HCl/Acetaminophen) versus ULTRAM® (tramadol HCl) versus Placebo in Subjects with Pain Following Oral Surgery

(CAPSS-241)

SYNOPSIS

Principal Investigator:
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Study Dates:
Study Initiation Date: November 8, 2002
Study Completion Date: February 7, 2003

Objective:

The objective of this study was to establish that ULTRACET™ is superior to ULTRAM® in analgesic efficacy for the treatment of pain following oral surgery.

Study Design:

This was a single-center, randomized, double-blind, placebo-controlled, single-dose, parallel study of subjects experiencing pain following an oral surgical procedure. The study consisted of 2 phases: screening and double-blind. Subjects who had at least moderate pain on a Pain Visual Analog Scale (PVA ≥50 mm on a 100 mm PVA Scale where 0 mm="No Pain" and 100 mm="Extreme Pain") and a 4-point Pain Intensity Scale (0=none, 1=mild, 2=moderate, 3=severe) within 5 hours following extraction of 2 or more impacted third molars (bone removal was required from at least 2 of the impacted third molars) were eligible for entrance into the double-blind phase. Approximately 450 subjects were to be randomized equally to 1 of 3 treatment groups [ULTRACET™ (75.0 mg tramadol HCl/650 mg acetaminophen), ULTRAM® (100 mg tramadol HCl) or placebo]. Subjects received a single dose of study medication, consisting of 2 capsules.

Pain intensity (intensity of current pain) was to be obtained prior to dosing using the pain intensity scale. Pain intensity and pain relief ratings (relief from starting pain) were to be obtained at 30 minutes and at 1, 2, 3, 4, 5 and 6 hours after receiving the dose of study medication. Pain relief was assessed using a 5-point Likert scale consisting of 4=complete, 3=a lot, 2=some, 1=a little and 0=none.

At any time during the 6-hour observation period, the subject could choose to receive a supplemental pain medication. Subjects were required to remain at the study facility for the entire 6-hour observation period, even if supplemental pain medication was taken.

Efficacy Variables:

The primary efficacy variables were the analgesic summary measures of total pain relief (TOTPAR), sum of pain intensity differences (SPID) and sum of total pain relief and sum of pain intensity differences (SPRID). Secondary efficacy variables included hourly pain relief (PAR), hourly pain intensity difference (PID), times to onset of perceptible and meaningful pain relief, incidence of and time to remedication with supplemental pain medication, and the subject's overall assessment of study medication.

Safety Variables:

Safety evaluations included assessment of vital sign measurements and the monitoring of adverse events.

Demographic and Baseline Characteristics:

A total of 456 subjects were randomized into the study. There were approximately twice as many females (63.6%) as males (36.4%). The ages ranged from 18 to 49 years with the mean age being 21.8 years. The majority of the subjects were White (89.0%) and had removal of 4 third molars (82.9%). The mean amount of bone removal was 2.1 (0=none, 1=minimal, 2=moderate, 3=substantial bone removal). The mean baseline PVA score was 72.2 mm, with the majority of subjects (68.6%) reporting moderate baseline pain and 31.4% of subjects reporting severe baseline pain. There were no statistically significant or clinically meaningful differences among the treatment groups for any of the demographic or baseline characteristics.

Discontinuation/Completion Information:

A total of 441 (96.7%) subjects completed the study per the protocol definition. Subjects were considered to have completed the study if any of the following were true:

- Subject had completed the 6-hour observation period without the use of supplemental pain medication; or
- Subject had no analgesic response to the study medication and had completed at least 1 hour of the observation period without the use of supplemental pain medication; or
- Subject had an analgesic response to the study medication and had completed at least 1 hour of the observation period and waited until the pain intensity returned to the same as at baseline before taking supplemental pain medication.

The number of subjects completing the study was similar for all treatment groups. Among the subjects who completed the study, the number of subjects that did not take supplemental medication was higher in the ULTRACET group (44.4%) than in the ULTRAM and placebo groups (15.8% and 9.3%, respectively).

Efficacy Results:

ULTRACET was statistically superior to ULTRAM and placebo for the 3 primary efficacy variables, TOTPAR, SPID and SPRID, and for all the secondary efficacy variables.

For the 3 primary efficacy variables, TOTPAR, SPID and SPRID, ULTRACET was statistically superior compared to ULTRAM and placebo at the 0-3 hour, 3-6 hour and 0-6 hour intervals ($p<0.001$ for all). Analysis of secondary efficacy variables also demonstrated statistically superior efficacy for ULTRACET compared to ULTRAM and placebo. ULTRACET was statistically superior compared to ULTRAM and placebo for PAR and PID at each time point during the 6-hour observation period ($p<0.001$). In addition, ULTRACET was statistically superior compared to ULTRAM and placebo for times to perceptible and meaningful pain relief ($p<0.001$ for both), incidence of and time to use of supplemental pain medication ($p<0.001$ for both), and subject's overall assessment of study medication ($p<0.001$).

ULTRAM was numerically superior to placebo for the 3 primary efficacy variables although the differences were not statistically significant. For the secondary efficacy variables, ULTRAM was statistically superior compared to placebo for time to meaningful pain relief and for PID and PAR at the 2-hour time point. In addition, ULTRAM was numerically superior compared to placebo for incidence of and time to use of supplemental pain medication, subject's overall assessment of study medication and PID and PAR (at all time points except 0.5 hours); however, the differences were not statistically significant.

Safety Results:

Of the 456 subjects in the Evaluable-for-Safety population, 238 (52.2%) experienced 1 or more adverse events. The number of subjects experiencing adverse events was higher in the ULTRACET and ULTRAM treatment groups (53.6% and 63.8%, respectively) than in the placebo group (39.1%). The most commonly reported adverse events in the ULTRACET and ULTRAM groups were nausea, dizziness, vomiting, headache and hot flushes. The incidence of nausea was statistically lower in the ULTRACET group (32.7%) compared to the ULTRAM group (46.1%;

p=0.019). In addition, the incidences of dizziness and vomiting were numerically lower in the ULTRACET group (22.2% and 18.3%, respectively) compared to the ULTRAM group (25.0% and 21.7%, respectively); however the differences were not statistically significant.

One subject each in the ULTRACET and ULTRAM groups (hemorrhage NOS and nausea, respectively) were discontinued from the study due to an adverse event. There were no deaths or serious adverse events during the study.

Conclusions:

This study demonstrates that ULTRACET is superior to ULTRAM in analgesic efficacy for the treatment of pain following oral surgery.

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