PriCara, Unit of Ortho-McNeil, Inc.

Clinical Study Report

A Comparison of the Efficacy and Safety of Tramadol HCl / Acetaminophen Versus Hydrocodone Bitartrate / Acetaminophen Versus Placebo in Subjects with Acute Musculoskeletal Pain

Protocol CAPSS-216; Phase IIIb

RWJ-26898-002/RWJ-03465
(Tramadol HCl/acetaminophen)

PRINCIPAL INVESTIGATOR: Multicenter

DATE STUDY INITIATED:
16 January 2003

DATE STUDY COMPLETED:
27 October 2004

Issue/Report Date: 16 September 2005
Department: Medical Affairs
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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

SYNOPSIS

NAME OF SPONSOR/COMPANY: PriCara, Unit of Ortho-McNeil, Inc. NAME OF FINISHED PRODUCT: ULTRACET® (tramadol HCl/acetaminophen) NAME OF ACTIVE INGREDIENT(S): (±)-cis-2-[(dimethylamino) methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride/acetaminophen	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: CAPSS-216 **Title of Study:** A Comparison of the Efficacy and Safety of Tramadol HCl/Acetaminophen Versus Hydrocodone Bitartrate/Acetaminophen Versus Placebo in Subjects with Acute Musculoskeletal Pain		
Principal Investigators: Multicenter, 47 Investigators		
Publication (Reference): Not applicable		
Initiation Date: 16 January 2003 **Completion Date:** 27 October 2004		**Phase of development:** IIIb

Objectives: The objective of this study was to compare the analgesic efficacy and safety of tramadol HCl/acetaminophen versus hydrocodone bitartrate/acetaminophen versus placebo for the treatment of acute musculoskeletal pain from an ankle sprain with a partial ligament tear.

Methodology: This was a multicenter, randomized, double-blind, inpatient/outpatient, active-controlled, placebo-controlled, parallel-group study comprised of 2 phases: Baseline and Double-Blind. Approximately 600 subjects experiencing acute musculoskeletal pain due to an ankle sprain severe enough to require prescription medication were enrolled. Subjects were randomized in a 1:1:1 ratio to receive either tramadol HCl/acetaminophen or hydrocodone bitartrate/acetaminophen or placebo.

Subjects who completed the Baseline Phase, met all inclusion/exclusion criteria, met the pain scale requirements and were appropriate for pain management with an oral analgesic could enter the Double-Blind Phase. The pain scale requirements were as follows: the subject had at least moderate pain due to acute musculoskeletal pain from an ankle sprain with a partial ligament tear [Pain Visual Analog Scale (PVA) $\geq$ 50 mm **and** had at least moderate pain on the Pain Intensity Scale] at Baseline and again immediately prior to the first dose of study medication.

Subjects were required to remain at the study site for 4 hours after the administration of study medication. Subjects completed the PVA Scales, Pain Relief Rating Scales and Pain Intensity Scales at 1, 2, 3 and 4 hours after the first dose of study medication. Subjects were not to bear weight on the injured leg or perform other activities immediately prior to the pain assessments that could have potentially affected the subjects' ankle pain. On Day 1, after the 4-hour evaluations, subjects were dispensed study medication for use throughout the remainder of the study. Subjects also evaluated and recorded in a daily diary, the pain intensity ratings and pain relief scores for Days 1-5 of the Double-Blind Phase.

At any time during the Double-Blind Phase, the subject could have chosen to receive a supplemental analgesic medication. If there was no analgesic response to the first dose of study medication, the subject was encouraged (but not required) to wait at least 1 hour before taking supplemental analgesic medication. Subjects who took supplemental analgesic medication were to be discontinued from the study. During the 4 hours after the first dose, if a supplemental analgesic medication was requested by the subject or if the subject required treatment with an anti-emetic medication, a final PVA, Pain Intensity and Pain Relief Rating Scales, and an Activity Impairment Assessment was made prior to the subject's taking supplemental analgesic or anti-emetic medication. Subjects who received supplemental analgesic or anti-emetic medication at this time were considered discontinued from the study, however, they remained at the study facility for 4 hours after the administration of study medication.

During the 4-hour post-dose evaluations at the study site, standard care related to the ankle sprain, with the exception of cold therapy, was used (e.g., rest, compression, elevation, use of crutches, etc.). Cold therapy to the injured ankle was not allowed during the 30-minute period preceding any pain evaluation or activity assessment at Baseline and during the 4-hour stay at the study site. Cold therapy could be used for approximately 15-20 minutes after pain evaluations, provided the cold therapy was discontinued at least 30 minutes prior to the next evaluation/assessment.

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After subjects completed the 4-hour post-dose evaluations at the study site, standard care related to the ankle sprain was used (e.g., rest, application of cold therapy, compression, elevation, use of crutches, etc.).

At the Final Visit (Day 6), subjects who took study medication for the entire study, completed the Pain Intensity and Pain Relief Rating Scales, an Activity Impairment Assessment and a Subject Overall Medication Assessment.

Number of Subjects (planned and analyzed): A total of 600 subjects were planned for entry into the study; a total of 603 subjects were randomized (192 tramadol HCL/acetaminophen, 204 hydrocodone bitartrate/acetaminophen, and 207 placebo). The Intent-to-Treat and modified Intent-to-Treat populations included 601 and 596 subjects, respectively. The Evaluable-for-Safety population (those subjects who took at least 1 dose of study medication and for whom at least 1 post-dose safety measurement was available) included 602 subjects.

Diagnosis and Main Criteria for Inclusion: The study was conducted in subjects between 18 and 75 years of age, with acute musculoskeletal pain from an ankle sprain with a partial ligament tear within 48 hours of the first study related procedure. Subjects must have had moderate pain from the ankle sprain defined as a PVA ≥ 50 mm and a Pain Intensity Scale rating of at least moderate, when evaluated at Baseline and immediately prior to the first dose of study medication.

Test Product, Dose and Mode of Administration, Batch No.: The test product consisted of 2 capsules of 37.5 mg tramadol HCl/325 mg acetaminophen (Batch Numbers R11971 or R12783) that were administered orally.

Reference Therapy, Dose and Mode of Administration, Batch No.: Reference therapy for the hydrocodone bitartrate/acetaminophen group consisted of 1 capsule of 7.5 mg hydrocodone bitartrate/650 mg acetaminophen (Batch numbers R11973 or R12785) and 1 capsule of identically matching placebo (Batch numbers R11972 or R12784) that were administered orally. Reference therapy for the placebo group consisted of 2 identically matching capsules of placebo (Batch numbers R11972 or R12784) that were administered orally.

Duration of Treatment: The planned duration of the Double-Blind Phase was approximately 6 days.

Criteria for Evaluation:

Efficacy: The primary efficacy parameter was Total Pain Relief (TOTPAR) over 4 hours on Day 1 after the administration of the first dose of study medication.

Secondary efficacy parameters were Sum of Pain Intensity Differences (SPID) over 4 hours, Sum of Total Pain Relief and Pain Intensity Differences (SPRID) over 4 hours, PVA Scores over 4 hours, mean daily pain intensity for Days 1-5, mean daily pain relief for Days 1-5, final pain intensity, final pain relief, final Activity Impairment Assessment, time to discontinuation due to lack of efficacy and Subject Overall Medication Assessment.

Safety: Safety was assessed by vital sign measurements, brief physical examination and evaluation of adverse events. Urine pregnancy tests were performed on women of child-bearing potential.

SYNOPSIS (CONTINUED)

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Statistical Methods: The efficacy analyses datasets consisted of:

- Intent-to-Treat population (ITT): included all randomized subjects who took at least 1 dose of study medication and provided at least 1 post-randomization efficacy measure.
- Modified Intent-to-Treat population (mITT): excluded those subjects who, after having an ankle X-ray performed after the 4-hour post dose evaluation period, were found to have a complete ligament tear, signs of talus displacement, bone fracture or multiple avulsion fractures.

The mITT population was the primary efficacy population.

The primary efficacy variable was Total Pain Relief (TOTPAR) over 4 hours on Day 1 after the administration of the first dose of study medication. The primary analysis was based on an analysis of covariance (ANCOVA) model with treatment and center as qualitative factors, and baseline pain intensity score as covariate. Model sensitivity was considered established if the hydrocodone bitartrate/acetaminophen group separated significantly ($p \leq 0.05$) from the placebo group in terms of TOTPAR value measured over the first 4 hours. The comparison of mean TOTPAR values between the tramadol HCl/acetaminophen group and the placebo group was tested at the significance level of 0.05.

SUMMARY

DISPOSITION OF STUDY SUBJECTS:

Of the 603 subjects randomized, a total of 523 (86.7%) subjects completed the study, 166 subjects (86.5%) in the tramadol HCl/acetaminophen group, 180 (88.2%) subjects in the hydrocodone bitartrate/acetaminophen group and 177 subjects (85.5%) in the placebo group. The most common reasons for early discontinuation in the tramadol HCl/acetaminophen group were adverse events and lack of efficacy with 10 subjects each (5.2%), citing either of these reasons. The most common reason for early discontinuation in the hydrocodone bitartrate/acetaminophen group was adverse event with 9 (4.4%) subjects discontinuing for this reason. The most common reason for early discontinuation in the placebo group was lack of efficacy with 21 (10.1%) subjects discontinuing for this reason.

DEMOGRAPHICS AND BASELINE CHARACTERISTICS:

Of the 596 subjects in the mITT population, 315 (52.9%) were male and 281 (47.1%) were female. The subjects ranged in age from 18 to 81 years (mean age 31.8 years); 282 subjects (47.3%) were White, 210 subjects (35.2%) were Black and 85 subjects (14.3%) were Hispanic.

SYNOPSIS (CONTINUED)

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EFFICACY RESULTS:

Tramadol HCl/acetaminophen was statistically superior to placebo for the primary efficacy variable, TOTPAR ($p < 0.001$). There was no statistical difference observed between tramadol HCl/acetaminophen and hydrocodone bitartrate/acetaminophen ($p = 0.608$). Model sensitivity was considered established because the hydrocodone bitartrate/acetaminophen group separated significantly ($p<0.001$) from the placebo group in terms of TOTPAR measured over the first 4 hours. All variables were evaluated in the mITT and ITT populations and the results were similar for both populations.

Based on the subject responder rate, tramadol HCl/acetaminophen and hydrocodone bitartrate/acetaminophen provided better pain relief overall, and at hours 1, 2, 3 and 4 than placebo. Tramadol HCl/acetaminophen produced significantly better pain relief than placebo based on average daily pain relief scores ($p=0.001$) for Days 1 to 5. Similarly, hydrocodone bitartrate/acetaminophen produced significantly better daily pain relief than placebo ($p<0.001$) based on average daily pain relief scores. No significant differences in daily pain relief scores ($p=0.492$) were observed between the tramadol HCl/acetaminophen group and the hydrocodone bitartrate/acetaminophen group. No significant differences were observed among the 3 treatment groups for average pain intensity scores and final visit activity impairment assessment scores. The subjects' overall assessment of study medication was significantly superior for tramadol HCl/acetaminophen versus placebo ($p=0.014$) and for hydrocodone bitartrate/acetaminophen versus placebo ($p=0.001$). There was no statistically significant difference between the two active treatment groups.

The incidence of efficacy failure (defined as the need for supplemental analgesic medication or discontinuing due to efficacy failure) in the hydrocodone bitartrate/acetaminophen group (2.5%) was significantly lower than in the placebo group (11.2%; $p=0.002$). No significant difference in the incidence of efficacy failure was observed between the tramadol HCl/acetaminophen and the hydrocodone bitartrate/acetaminophen groups ($p=0.089$) and between the tramadol HCl/acetaminophen and the placebo groups ($p=0.081$). Subjects receiving tramadol HCl/acetaminophen had similar incidences of time to efficacy failure both during the first 4 hours ($p=0.706$) and over all study days ($p=0.125$) when compared to placebo for time to efficacy failure. The hydrocodone bitartrate/acetaminophen group, when compared to placebo, was statistically significant both during the first 4 hours ($p=0.036$) and over all study days ($p=0.001$) for time to efficacy failure. There was no statistically significant difference between the tramadol HCl/acetaminophen group and the hydrocodone bitartrate/acetaminophen group for the first 4 hours ($p=0.078$) and over all study days ($p=0.063$) for time to efficacy failure. The Kaplan-Meier estimates of the cumulative discontinuation rates due to lack of efficacy or due to an adverse event were as follows: between the tramadol HCl/acetaminophen group and the placebo group ($p=0.719$); between the tramadol HCl/acetaminophen group and the hydrocodone bitartrate/acetaminophen group ($p=0.101$); and between the hydrocodone bitartrate/acetaminophen group and the placebo group ($p=0.045$).

SYNOPSIS (CONTINUED)

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Summary and Analysis of Total Pain Relief
(Modified Intent-to-Treat - Study CAPSS-216)

	Tram/APAP (N=190)	Hyd/APAP (N=201)	Placebo (N=205)	Tram/APAP vs Hyd/APAP	p-value[b] for Placebo	Hyd/APAP vs Placebo
TOTPAR						
n	189	201	205			
Mean	6.6	6.8	5.4	0.608	< 0.001	< 0.001
Median	6	7	5			
SD	3.35	3.65	3.69			
(Min, Max)	(-2, 14)	(-4, 17)	(-4, 17)			

SAFETY RESULTS:

Of the 602 subjects in the Evaluable-for-Safety population, 83 subjects (43.2%) in the tramadol HCl/acetaminophen group, 74 subjects (36.5%) in the hydrocodone bitartrate/acetaminophen group and 40 subjects (19.3%) in the placebo group experienced adverse events. Somnolence was the most commonly reported adverse event in all 3 treatment groups, with incidences of 17.2%, 16.3%, and 6.8% in the tramadol HCl/acetaminophen group, the hydrocodone bitartrate/acetaminophen group and the placebo group, respectively. The other common adverse events in all 3 treatment groups were nausea (15.1% in the tramadol HCl/acetaminophen group, 14.3% in the hydrocodone bitartrate/acetaminophen group, and 3.4% in the placebo group), dizziness (8.9%, 9.4% and 1.4%, respectively) and vomiting (7.3%, 3.9% and 1.0%, respectively). The majority of adverse events in all 3 treatment groups were mild to moderate in severity.

Ten subjects (5.2%) in the tramadol HCl/acetaminophen group, 9 subjects (4.4%) subjects in the hydrocodone bitartrate/acetaminophen group and 3 subjects (1.4%) in the placebo group discontinued treatment due to an adverse event. No clinically significant changes in mean values for vital signs in any of the 3 groups were observed. No serious adverse events were reported.

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Adverse Events – Overall Summary
(Evaluable-for-Safety – Study CAPSS-216)

	Tram/APAP (N=192) n (%)	Hyd/APAP (N=203) n (%)	Placebo (N=207) n (%)
Number (%) of subjects with any adverse event regardless of relationship to study drug	83 (43.2)	74 (36.5)	40 (19.3)
Number (%) of subjects with any adverse event related to study drug[a]	78 (40.6)	72 (35.5)	29 (14.0)
Number (%) of subjects with any adverse event causing withdrawal from study	10 (5.2)	9 (4.4)	3 (1.4)
Number (%) of subjects with any serious adverse event	0 (0.0)	0 (0.0)	0 (0.0)
Number (%) of subjects with any serious adverse event related to study drug[a]	0 (0.0)	0 (0.0)	0 (0.0)
Number (%) of subjects who died	0 (0.0)	0 (0.0)	0 (0.0)

[a] An event was related if its relationship to study medication was possible, probable or very likely.

CONCLUSION:

The results of this study demonstrate that tramadol HCl/acetaminophen is safe and effective for the treatment of acute musculoskeletal pain from an ankle sprain with a partial ligament tear. Tramadol HCl/acetaminophen and hydrocodone bitartrate/acetaminophen both showed superior efficacy when compared to placebo for the treatment of acute musculoskeletal pain from an ankle sprain. The safety profile seen in this study was consistent with that previously observed for tramadol HCl/ acetaminophen.

Date of the report: 16 September 2005

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