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PROPRIETARY DRUG NAME/INN: Celebrex[®] / Celecoxib

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI

PROTOCOL NO.: A3191064

PROTOCOL TITLE: A multicenter, randomized, double-blind, double-dummy study of the safety, tolerability and efficacy of celecoxib 200 mg twice a day (with a 400 mg attack dose) versus sodium diclofenac 75 mg twice a day in subjects with acute low back pain.

Study Center(s): Nine (9) centers in Brazil

Study Initiation and Completion Dates: 01 October 2003 to 06 October 2004

Phase of Development: Phase 4

Study Objective(s):

Primary: To evaluate analgesic efficacy of celecoxib versus diclofenac sodium (diclofenac) in subjects with acute low back pain

Secondary: To evaluate safety and tolerability of celecoxib compared with diclofenac in the treatment of acute low back pain

METHODS

Study Design: This was a multicenter, randomized, parallel group, double-blind, double dummy, active comparator study. Eligible subjects were randomized to either celecoxib 200 mg twice daily (BID) or diclofenac 75 mg BID. A total of 3 visits were planned during a 7-day evaluation period. First visit at baseline, second visit Day 3 and a third visit at Day 7.

Number of Patients (planned and analyzed):

Planned: 240 subjects (120 in each treatment group)

Analyzed: 244 subjects (123 in the celecoxib group and 121 in the diclofenac group)

Diagnosis and Main Criteria for Inclusion: This study included male or female subjects, aged between 18 and 65 years, of general good health who had a diagnosis of acute low back pain that fell into the 1st or 2nd category of the “Quebec Task Force” classification for acute low back pain of moderate to severe intensity (greater than 50 mm in the visual analog scale [VAS] 0-100 mm). Subjects were to have had acute low back pain onset less than 72 hours prior to inclusion and greater than 6 weeks after the last acute low back pain episode.

Study Treatment: On Day 1 of the study, subjects randomized to celecoxib received an attack dose of 400 mg, followed by a dose of 200 mg with the evening meal only if the interval between the first dose and the evening dose was ≥ 4 hours. Subjects randomized to diclofenac received a 75 mg dose at the study center followed by a second 75 mg dose, irrespective of the time since the first dose, with their evening meal. For the remaining 6 days, subjects received celecoxib 200 mg BID or diclofenac 75 mg BID throughout the study. Both study treatments and matched placebo were supplied in capsule form.

Efficacy Evaluations:

Primary: Change from Baseline at Day 3 in the patient rated VAS Pain Intensity assessment

Secondary: Change from Baseline at Day 7 in VAS Pain Intensity assessment; Categorical Pain Intensity (0 = no pain to 3 = severe pain); Pain Relief (0 = none to 4 = total); and Global Subject's Assessment (1 = unsatisfactory to 4 = excellent) on Days 3 and 7

Other Evaluations: Subject's functional ability as measured by the change from baseline to Day 7 in the "Roland Morris" Questionnaire and the subjects' health and quality of life as measured by the change from baseline to Day 7 in the Acute SF-36 (8 domains).

Safety Evaluations: Physical examination, vital signs and adverse events (AEs) were evaluated on Days 3 and 7 or on early discontinuation.

Statistical Methods:

Three subject populations were defined:

- Modified intent-to-treat population (MITT): All randomized subjects who received at least one dose of study medication and had at least one post-baseline efficacy assessment
- Per protocol (PP): All subjects in the MITT population who met key inclusion and did not violate key exclusion criteria, had a Day 3 VAS, took study medication appropriately up to and including Day 3, did not take any rescue medication prior to Day 3 and with no major protocol violations
- Safety: All subjects who received at least one dose of study medication

The PP population was used for the analysis of the primary efficacy measure only, the MITT population was used for sensitivity analysis for the primary measure and analysis of all secondary efficacy measures and the safety population was used for demographic and safety analyses.

Efficacy: For the primary efficacy measure, the change from baseline at Day 3 in the subject rated 0-100 mm VAS, was analyzed using an analysis of covariance (ANCOVA) model with effects for treatment, center (fixed), and the baseline assessment as the covariate applied to the per protocol population. This model was used to construct a two-sided 95% confidence interval (95% CI) for the treatment difference (diclofenac - celecoxib). Celecoxib would be declared as

non-inferior to diclofenac if the lower bound of the two-sided 95% CI of the treatment difference is greater than -10 mm.

Treatment differences for the secondary efficacy variables at Days 3 and 7 were analyzed using an analysis of variance (ANOVA) model with effects for treatment, center (fixed), and baseline measurements. This model was used to construct a two-sided 95% CI for the treatment difference (diclofenac - celecoxib). There was no pre-specified non-inferiority margin for secondary efficacy variables.

Safety: All AEs reported during treatment and for up to 30 days after the final dose of study medication were included as treatment-emergent AEs.

RESULTS

Subject Disposition and Demography: A summary of subject disposition is presented in Table S1, below.

Table S1 Subject Disposition

	Celecoxib	Diclofenac
Randomized	123	121
Completed	118 (95.9%)	119 (98.3%)
Withdrawn	5 (4.1%)	2 (1.7%)
Adverse event	3 (2.4%)	2 (1.7%)
Protocol deviation	1 (0.8%)	0 (0.0%)
Laboratory abnormality	1 (0.8%) ^a	0 (0.0%)

^aReported as an adverse event; occurred before any dose of study medication had been taken.

The majority of subjects were young and middle-aged adults. Mean age was 40.6 years in the celecoxib group and 39.6 years in the diclofenac group with an overall age range of 18 to 68 years. In both groups the majority of subjects were female: 85 (69.1%) in the celecoxib group and 66 (54.5%) in the diclofenac group. The race distribution was balanced in both groups. The majority of patients in each treatment group were white (85 [69.1%] in the celecoxib group and 84 [69.4%] in the diclofenac group).

In general, all baseline measurements showed similar distributions in the both groups even though no statistical tests were conducted to compare demographic and other characteristics at baseline.

Efficacy Results: The results of the primary efficacy analysis are presented for the PP and MITT populations in Table S2.

Table S2 Change in VAS Pain Intensity

	Celecoxib	Diclofenac
Per Protocol Population		
LS mean change in VAS Pain Intensity from Baseline to Day 3	40.00 mm	42.55 mm
Difference in least squares means	-2.56 mm	
95% confidence interval for the difference	-7.67 mm, 2.56 mm	
Modified Intent-to-Treat Population		
Difference in least squares means	-2.62 mm	
95% confidence interval for the difference	-7.55 mm, 2.31 mm	

VAS: Visual Analogue Scale.

Results from the secondary efficacy analyses are summarized in Table S3, below.

Table S3 Summary of Secondary Efficacy Results (MITT Population)

Mean change from Baseline in	Day 3 Difference^a (95% CI)	Day 7 Difference^a (95% CI)
VAS	-2.62 mm (-7.55 mm, 2.31 mm)	-1.93 mm (-7.52 mm, 3.66 mm)
Categorical Pain Intensity score	-0.09 (-0.25, 0.06)	-0.05 (-0.25, 0.14)
Pain relief score	0.22 (0.01, 0.44)	0.10 (-0.18, 0.37)
Subject Global Assessment score	0.03 (-0.17, 0.22)	0.11 (-0.11, 0.32)

^aDifference = diclofenac – celecoxib.

Other Results: Results of the Roland Morris questionnaire on disability and lower back pain are summarized in Table S4.

Table S4 Summary of Assessments of Roland Morris Questionnaire on Disability and Lower Back Pain (MITT Population)

	Celecoxib	Diclofenac
Change from Baseline to Day 7	-7.90	-8.23
Least squares mean difference ^a (95% CI)	0.32 (-1.54, 0.89)	

^aDifference = diclofenac – celecoxib.

The subjects' health and quality of life was assessed using the Acute SF-36 Questionnaire evaluations. The absolute scores of all 8 domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health) showed no statistical differences at baseline ($p > 0.05$ for all domains). The changes from Baseline to Day 7 in all 8 domains showed similar improvement in both treatment groups, with no statistically significant differences between treatment groups.

Safety Results: Overall, 46 subjects, 20 in the celecoxib group and 26 in the diclofenac group, reported at least one AE during the study. The majority of AEs were mild or moderate in intensity with only 1 subject (0.8%) in the celecoxib group and 3 subjects (2.5%) in the diclofenac group experiencing severe AEs. All AEs reported in more than 1% of subjects in either treatment group are presented in Table S5.

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Table S5 Treatment-Emergent Adverse Events (All Causalities) Reported in >1% of Subjects in Either Treatment Group

Adverse Event	Celecoxib (n=123) n (%)	Diclofenac (n=121) n (%)
Subjects reporting at least 1 AE	20 (16.3)	26 (21.5)
Abdominal pain upper	6 (4.9)	6 (5.0)
Gastritis	2 (1.6)	5 (4.1)
No therapeutic response	2 (1.6)	5 (4.1)
Somnolence	2 (1.6)	4 (3.3)
Diarrhea	1 (0.8)	4 (3.3)
Nausea	2 (1.6)	1 (0.8)
Hyperhidrosis	2 (1.6)	0

There were no deaths or serious AEs reported in this study.

Six subjects withdrew from the study due to adverse events: four (3.3%) in the celecoxib group and two (1.7%) in the diclofenac group.

Four (3.3%) subjects who received celecoxib discontinued from study due to a total of five AEs (somnolence, hypersensitivity, dizziness, gastroenteritis and glutamic-pyruvate transaminase increased). With the exception of glutamic-pyruvate transaminase increased, these AEs were considered to be related with the study drug.

Two 2 subjects who received diclofenac discontinued from the study due AEs of acute gastritis (one subject) and vertigo (one subject). Both events were considered to be related to treatment.

Overall, there were no clinically important differences across treatment groups with respect to changes from Baseline in weight or vital signs with the exception of two hypertensive subjects in the celecoxib group with clinically relevant decreases in systolic / diastolic pressure and one hypertensive subject with clinically significant increases in systolic / diastolic pressure. None of these clinically significant changes was considered to be related to study treatment.

CONCLUSION(S):

Overall, celecoxib 400 mg with a second dose of 200 mg on the first day, followed by 200 mg BID thereafter was observed to be as efficacious as diclofenac 75 mg BID in treating the signs and symptoms of acute Low Back Pain. Celecoxib and diclofenac improved to the same extent the subjects' health, quality of life and disability due to acute low back pain. Both treatments, at the studied dosages, were generally safe and well tolerated.

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