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Prescribing decisions should be made based on the approved package insert

Link to drug label

Proprietary Drug Name	**INN**	**Therapeutic area and FDA approved indications**
Celebrex	Celecoxib	Relief of signs and symptoms of osteoarthritis Relief of signs and symptoms of rheumatoid arthritis in adults Management of acute pain in adults Treatment of primary dysmenorrhea Reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis as an adjunct to usual care

Name of Sponsor/Company: Pfizer Inc.

Title of Study: COXA-0508-249

A Double-Blind, Randomized, Three Arm, Two Period, Crossover Study to Compare Celecoxib, Acetaminophen, and Placebo in Patients with Osteoarthritis of the Hip or Knee

Study centre(s): 61 study sites in the United States

Publication (reference, if applicable): See attached bibliography.

Studied period 30 May 2002 - 27 Nov 2002 | **Phase of development:** Phase 4

Objectives: The primary objective of this study was to evaluate the efficacy and safety of celecoxib, acetaminophen, and placebo in a randomized, double-blind, crossover clinical trial in ambulatory patients with osteoarthritis (OA) of the hip or knee.

Methodology: Patients meeting the inclusion and exclusion criteria underwent an initial washout period of three to seven days after which they were randomly assigned to receive either celecoxib 200 mg QD, acetaminophen 1000 mg QID, or placebo for six weeks. After the initial six-week treatment period, patients underwent another three- to seven-day washout period, after which they were assigned to one of the other two treatments for the second six-week treatment period. Patients could not receive the same study medication in Period 2 as in Period 1, as shown in the table below (with approximate planned sample sizes in parentheses):

Period 1 Treatment	Washout	Period 2 Treatment
Celecoxib 200 mg QD (n=186)	3 to 7 Days	Acetaminophen 1000 mg QID (n=124) *or* Placebo (n=62)
Acetaminophen 1000 mg QID (n=186)	3 to 7 Days	Celecoxib 200 mg QD (n=124) *or* Placebo (n=62)
Placebo (n=186)	3 to 7 Days	Celecoxib 200 mg QD (n=124) *or* Acetaminophen 1000 mg QID (n=62)

Patients who were not taking an NSAID and/or analgesic therapy to control their arthritis symptoms at Screening were not required to undergo an initial washout period before entering the trial. Efficacy was assessed using standard measures of pain, physical function, and quality of life in arthritis trials. Safety was assessed using standard monitoring of adverse events and laboratory tests.

Number of patients (planned and analyzed): The planned enrollment was approximately 558 patients. A total of 556 patients were enrolled and randomized to treatment, and all randomized patients received study medication. Therefore, the Intent-to-Treat (ITT) Cohort in Period 1 consisted of 189 patients receiving celecoxib 200 mg QD, 185 receiving acetaminophen 1000 mg QID, and 182 receiving placebo. Disposition of patients into the six possible treatment sequences is shown below.

Period 1 Treatment	Period 2 Treatment	No. of Patients
Celecoxib	Acetaminophen	127
Acetaminophen	Celecoxib	123
Celecoxib	Placebo	62
Placebo	Celecoxib	119
Acetaminophen	Placebo	62
Placebo	Acetaminophen	63
		Total 556

In addition to the ITT Cohort, the Protocol-Adherent (PA) Cohort was used for analyses of the primary efficacy variable and the two principal reinforcing efficacy variables. The PA Cohort included 329 patients: 79 receiving celecoxib/acetaminophen, 80 receiving acetaminophen/celecoxib, 34 receiving celecoxib/placebo, 71 receiving placebo/celecoxib, 28 receiving acetaminophen/placebo, and 37 receiving placebo/acetaminophen.

Diagnosis and main criteria for inclusion: Patients were eligible for this study if they had documented OA of the hip or knee (Kellgren-Lawrence Grade 2-4) and, in the Investigator's opinion, required and were eligible for chronic (daily) therapy with an NSAID and/or analgesic.

Duration of treatment: Six weeks (42+3 days) per Treatment Period.

Test product, dose and mode of administration:
Celecoxib 200 mg capsules, administered 200 mg QD (with the morning meal).

Reference therapy, dose and mode of administration:
Acetaminophen 500 mg capsules administered 1000 mg QID (with meals and at bedtime).
Placebo tablets identical in size and appearance to the celecoxib capsules
Placebo tablets identical in size and appearance to the acetaminophen capsules.

Criteria for evaluation:

Efficacy: The primary measures of efficacy in this study were the Paired Preference score, by which the patient compared, at Visit 5, the drugs taken in the two treatment periods, the WOMAC Total Domain score, and the MDHAQ Pain score. Secondary efficacy variables were as follows:

1. The WOMAC pain, stiffness, and physical function subdomains.
2. The MDHAQ Patient's Assessment of Fatigue.
3. The MDHAQ Patient's Assessment of Global Status.
4. The MDHAQ GI Distress Scale.
5. The MDHAQ Basic ADL assessment.
6. Investigator Assessment of Global Status.
7. Investigator Assessment of Change in Global Status Since Previous Visit.
8. Patient Assessment of Helpfulness of the Study Drug.
9. Patient Assessment of Arthritis.
10. Investigator Assessment of Which Treatment Appeared Better for the Patient.
11. SF-36 Health Survey.

Tertiary efficacy variables were:

1. Paired Preference score stratified by Global Severity of OA at Screening (mild or moderate/severe).
2. WOMAC Total Domain score stratified by Global Severity of OA at Screening (mild or moderate/severe).
3. MDHAQ Pain score stratified by Global Severity of OA at Screening (mild or moderate/severe).
4. Correlation of Paired Preference score with each of the following:
    a. WOMAC Total Domain score;
    b. MDHAQ Pain score;
    c. MDHAQ Patient's Assessment of Global Status;
    d. Investigator Assessment of Global Status;
    e. Patient Assessment of Helpfulness of the Study Drug;
    f. Patient Assessment of Arthritis.

Safety: General clinical safety of study medication was monitored through reporting of adverse events, serious adverse events, and clinical laboratory test results.

Statistical methods: Analyses of Screening and Baseline data were performed using Fisher's Exact Test or chi-square test for categorical variables and Kruskal-Wallis Test for continuous variables.

Efficacy data were summarized by sequence group and by treatment group for both Treatment Periods 1 and 2.

Results in efficacy measures that were expressed as continuous variables (e.g., 100-mm visual analog scales) were analyzed for both Periods combined and for Periods 1 and 2 separately. For analyses incorporating both Periods, generalized estimating equations with period and treatment as fixed effects and Baseline scores of the patient, Baseline scores of the Period, and Screening scores as covariates, were used to compare the least square mean changes from Baseline. For single period analyses, general linear models were used comparing least square mean changes from Baseline among treatment groups, with center and treatment as fixed effects and Baseline and Screening scores as covariates.

Results in efficacy measures that were expressed as categorical variables (e.g., Paired Preference and Investigator Assessment of Which Treatment Appeared Better for the Patient) were analyzed using logistic regression techniques.

Tertiary analyses involving subgroups of patients were performed using methods identical to those used for the main analyses. Correlations of the Paired Preference results with other measures of efficacy were done using both Pearson and Spearman correlations.

The covariates in all efficacy analyses consisted of the Screening and Baseline scores of the variable being analyzed. Other factors were included as appropriate for the individual analyses. All hypothesis tests were conducted using a Type I error rate of 5%.

Overall percentages of patients experiencing adverse events were compared using Fisher's Exact test.

Summary

Disposition of Subjects and Baseline Characteristics:

The mean ages of patients varied from 62.7 to 64.8 across the six sequence groups (p=0.708). Proportions of female patients varied from 57.1% to 71.4% (p=0.410).

The six sequence groups were comparable with respect to medical history, patient status, and arthritis assessments at Baseline.

Efficacy Results:

Results in the primary and principal reinforcing efficacy variables are shown in the Tables below:

Paired Preference Results (Periods 1 and 2)

Preference	No. (%) of Patients	Odds Ratio	P Value
Celecoxib/acetaminophen and acetaminophen/celecoxib sequences			
Prefer celecoxib	95 (38.0)	1.47	0.009
Prefer acetaminophen	62 (24.8)		
No preference	93 (37.2)		
Total	250 (100)		
Celecoxib/placebo and placebo/celecoxib sequences			
Prefer celecoxib	76 (42.0)	2.47	<0.001
Prefer placebo	32 (17.7)		
No preference	73 (40.3)		
Total	181 (100)		
Acetaminophen/placebo and placebo/acetaminophen sequences			
Prefer acetaminophen	41 (32.8)	1.68	0.007
Prefer placebo	21 (16.8)		
No preference	63 (50.4)		
Total	125 (100)		
Global P value			<0.001

WOMAC Total Domain Results (Periods 1 and 2)

	Celecox/Acet	Acet/Celecox	Celecox/Pbo	Pbo/Celecox	Acet/Pbo	Pbo/Acet
Visit 2	52.4±17.1	51.2±17.4	51.4±19.0	51.2±20.3	52.5±17.4	54.9±18.4
Visit 3	39.4±22.4	42.3±21.6	36.6±19.9	45.7±25.0	45.0±19.3	51.8±20.6
Change	-12.9±19.3	-8.9±19.2	-14.8±17.6	-5.4±20.5	-7.5±14.6	-3.1±19.4
Visit 4	45.4±22.2	46.9±21.6	41.1±20.8	47.7±24.2	48.8±19.4	52.2±21.5
Visit 5	42.8±23.0	36.2±23.0	39.0±22.1	38.4±25.7	46.3±19.8	42.7±23.1
Change	-2.6±15.3	-10.7±19.0	-2.2±15.3	-9.3±17.4	-2.5±13.1	-9.4±14.6

P Values (both periods combined)*

		Difference in least-square means
Global:	<0.001	
Celecoxib vs acetaminophen:	<0.001	-4.62
Celecoxib vs placebo:	<0.001	-7.70
Acetaminophen vs placebo:	0.005	-3.08

* P values based on comparison of least-square mean changes from Baseline.
Celecox = Celecoxib, Acet = Acetaminophen, Pbo = Placebo

MDHAQ Pain Results (Periods 1 and 2)

	Celecox/Acet	Acet/Celecox	Celecox/Pbo	Pbo/Celecox	Acet/Pbo	Pbo/Acet
Visit 2	65.5±14.9	64.2±16.3	64.4±14.6	63.9±15.6	65.5±18.0	65.3±15.4
Visit 3	44.8±27.3	50.0±26.14	40.5±24.4	54.1±28.3	52.5±25.3	62.0±20.2
Change	-20.7±26.8	-14.2±23.6	-23.9±26.4	-9.8±27.9	-13.0±24.1	-3.3±24.3
Visit 4	55.9±25.9	54.9±25.5	50.5±24.8	56.6±26.8	58.1±24.1	59.7±23.0
Visit 5	49.8±27.8	42.5±27.9	50.9±27.0	43.0±29.5	53.8±24.5	45.8±25.7
Change	-6.1±24.9	-12.4±25.1	0.4±24.7	-13.6±25.3	-4.3±22.8	-14.0±21.5

P Values (both periods combined)*

Global:	<0.001	Difference in least-square means
Celecoxib vs acetaminophen:	<0.001	-5.87
Celecoxib vs placebo:	<0.001	-12.24
Acetaminophen vs placebo:	<0.001	-6.38

* P values based on comparison of least-square mean changes from Baseline.
Celecox = Celecoxib, Acet = Acetaminophen, Pbo = Placebo

Secondary efficacy variables supported the above results. In general across all variables, the largest improvements from Baseline in both Treatment Periods were seen in the celecoxib group, the smallest were seen with placebo, and improvements for acetaminophen were intermediate between the two. Almost all differences in disease-specific measures between celecoxib and placebo and between celecoxib and acetaminophen were statistically significant in favor of celecoxib. This was particularly evident in analyses of Periods 1 and 2 combined, in which the crossover design allowed patients to serve as their own controls. Most differences between acetaminophen and placebo were statistically significant in the two-period analyses; single-period analyses showed more instances in which acetaminophen failed to separate from placebo statistically, particularly in Period 2.

Safety Results:

Adverse event results from Periods 1 and 2 combined are shown in the following table:

Summary of Most Common Adverse Events (Periods 1 and 2 Combined)

Event	Celecoxib 200 mg QD (n=373)	Acetaminophen 1000 mg QID (n=331)	Placebo (n=273)
Any event	27.6%	26.3%	23.1%
Most common events (³ 1.5%)			
Peripheral edema	2.4	1.8	0.7
Nausea	2.1	1.2	1.1
Headache	1.9	2.7	2.6
Upper resp tract inf.	1.9	2.7	0.7
Constipation	1.6	0.3	1.1
Diarrhea	1.6	3.3	1.5
Dyspepsia	1.6	1.8	0.7
Injury accidental	1.6	1.8	1.8
Sinusitis	1.6	0.6	1.1
Abdominal pain	1.1	1.8	2.2
Tooth disorder	1.1	1.5	0.7
Any event causing withdrawal	3.5	3.6	2.6

* All entries are % of patients.

A total of four serious adverse events occurred: two cases of angina pectoris (one in each of the acetaminophen and placebo groups), a case of cholecystitis in a patient receiving celecoxib, and a case of unstable angina in a patient receiving celecoxib. No safety or tolerability concerns were evident from the laboratory data, and no substantial differences between the groups occurred in the Visit 3 analyses.

CONCLUSION:

Efficacy Conclusions:

- When asked to compare the two regimens, patients who had received both celecoxib and acetaminophen strongly preferred celecoxib over acetaminophen.
- Celecoxib was efficacious in treating OA of the hip or knee, with improvements in efficacy measures routinely found to be highly statistically significant compared with placebo.
- Acetaminophen generally showed larger improvements from Baseline than placebo. However, these differences were not consistently found to be statistically significant.
- The combined Period 1/Period 2 analyses showed celecoxib to be statistically significantly superior to acetaminophen in all primary efficacy variables. For the secondary efficacy variables, celecoxib was superior to acetaminophen in a substantial majority of the combined comparisons.

Safety Conclusions:

- All treatments were safe and well tolerated in this study.
- Overall incidences of adverse events and of adverse events causing withdrawal were very similar among the three groups.
- The frequency and character of the adverse events experienced by patients were consistent with events seen in other trials of similar populations and duration. No pattern of deleterious effect of treatment was suggested by the types of adverse events.
- No preponderance of severity of events was seen with active treatments.
- In both periods, patients receiving celecoxib reported less GI distress on the MDHAQ GI distress scale than patients in either the placebo or the acetaminophen group.
- Serious adverse events occurred with low frequency in all treatment groups.

Based on report completed: 11 August 2003