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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: Protocol 635-IFL-0508-010

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): 42 study sites in the United States.

Publication (reference, if applicable) See attached bibliography

Studied period: 19 Oct 2001 - 02 May 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 planned sample sizes in parentheses):

` Period 1	Treatment Washout	Period 2 Treatment
Celecoxib 200 mg QD (n=150)	3 to 7 Days	Acetaminophen 1000 mg QID (n=100) or Placebo (n=50)
Acetaminophen 1000 mg QID (n=150)	3 to 7 Days	Celecoxib 200 mg QD (n=100) or Placebo (n=50)
Placebo (n=150)	3 to 7 Days	Celecoxib 200 mg QD (n=100) or Acetaminophen 1000 mg QID (n=50)

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 450 patients.

A total of 524 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 181 patients receiving celecoxib 200 mg QD, 171 receiving acetaminophen 1000 mg QID, and 172 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	121
Acetaminophen	Celecoxib	114
Celecoxib	Placebo	60
Placebo	Celecoxib	115
Acetaminophen	Placebo	57
Placebo	Acetaminophen	57
	Total	**524**

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. For WOMAC Total Domain analyses in Period 1, the PA cohort included 348 patients: 121 receiving celecoxib, 115 receiving acetaminophen, and 112 receiving placebo. For MDHAQ Pain score analyses in Period 1, the PA Cohort included 354 patients: 123 receiving celecoxib, 116 receiving acetaminophen, and 115 receiving placebo. For analyses of Paired Preference scores (Periods 1 and 2), the PA Cohort included 273 patients: 63 receiving celecoxib/ acetaminophen, 52 receiving acetaminophen/celecoxib, 32 receiving celecoxib/placebo, 65 receiving placebo/celecoxib, 33 receiving acetaminophen/placebo, and 28 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 WOMAC Total Domain score and the MDHAQ Pain score in Treatment Period 1, and the Paired Preference score, by which the patient compared, at Visit 5, the drugs taken in the two treatment periods.

Secondary efficacy variables were as follows:

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

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 treatment group for Treatment Period 1 and by sequence group for Period 2.

Results in efficacy measures that were expressed as continuous variables (e.g., 100-mm visual analog scales) were analyzed for Period 1, and for both Periods combined. For Period 1 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. 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.

Results in efficacy measures that were expressed as categorical variables (e.g., Paired Preference and proportions of responders) were analyzed using logistic regression techniques.

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 were 64.1 years for celecoxib, 63.5 years for acetaminophen, and 62.6 years for placebo. Proportions of female patients were as follows: 61.3% for celecoxib, 62.6% for acetaminophen, and 64.5% for placebo.

The three treatment 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:

WOMAC Total Domain Results (Period 1)

	Celecoxib 200 mg QD	**Acetaminophen** 1000 mg QID	**Placebo**	**P Value***
ITT Cohort				
Visit 2	48.6 ± 19.6	52.8 ± 19.7	50.3 ± 20.8	
Visit 3	38.2 ± 23.1	44.4 ± 23.5	45.4 ± 24.0	
Change	-10.4 ± 20.6	-8.4 ± 19.7	-4.8 ± 21.6	Global: 0.008
				C vs A: 0.180
				C vs P: 0.002
				A vs P: 0.080
PA Cohort				
Visit 2	48.4 ± 18.4	53.7 ± 20.1	51.7 ± 20.8	
Visit 3	35.2 ± 22.1	44.9 ± 23.9	44.9 ± 23.6	
Change	-13.2 ± 20.3	-8.8 ± 21.0	-6.8 ± 23.0	Global: 0.008
				C vs A: 0.054
				C vs P: 0.002
				A vs P: 0.269

* P values based on comparison of least-square mean changes from Baseline. C=celecoxib, A=acetaminophen, P=placebo.

MDHAQ Pain Scores (Period 1)

	Celecoxib 200 mg QD	Acetaminophen 1000 mg QID	Placebo	P Value*
ITT Cohort				
Visit 2	62.0 ± 14.9	67.5 ± 15.2	64.0 ± 15.1	
Visit 3	43.0 ± 25.6	50.2 ± 27.1	53.5 ± 27.0	
Change	-19.0 ± 25.4	-17.4 ± 25.8	-10.5 ± 24.9	Global: 0.002
				C vs A: 0.193
				C vs P: <0.001
				A vs P: 0.031
PA Cohort				
Visit 2	62.1 ± 13.8	68.2 ± 14.7	63.6 ± 14.1	
Visit 3	39.5 ± 25.3	49.5 ± 27.0	50.3 ± 25.7	
Change	-22.6 ± 25.1	-18.6 ± 26.1	-13.2 ± 26.4	Global: 0.007
				C vs A: 0.049
				C vs P: 0.002
				A vs P: 0.277

* P values based on comparison of least-square mean changes from Baseline.

Paired Preference Results (Periods 1 and 2)

Preference	No. (%) of Patients		Odds Ratio	P Value
Celecoxib/acetaminophen and acetaminophen/celecoxib sequences				
Prefer celecoxib	66	(57.4)	2.47	<0.001
Prefer acetaminophen	24	(20.9)		
No preference	25	(21.7)		
Total	115	(100)		
Celecoxib/placebo and placebo/celecoxib sequences				
Prefer celecoxib	54	(55.7)	2.48	<0.001
Prefer placebo	24	(24.7)		
No preference	19	(19.6)		
Total	97	(100)		
Acetaminophen/placebo and placebo/acetaminophen sequences				
Prefer acetaminophen	22	(36.1)	1.01	0.977
Prefer placebo	18	(29.5)		
No preference	21	(34.4)		
Total	61	(100)		

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 were statistically significant, and most differences between celecoxib and acetaminophen were 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. Differences between acetaminophen and placebo were only sporadically found to be statistically significant.

Safety Results:

Adverse event results from Period 1 are shown in the following table:

Summary of Adverse Events (Period 1)

Event	Celecoxib 200 mg QD (n=181)	Acetaminophen 1000 mg QID (n=171)	Placebo (n=172)	
Any event		**40.9**	**43.9**	**41.3**
Most common events (≥2.5%)				
Upper respiratory tract inf.	6.6	8.2	4.7	
Dyspepsia	5.5	2.9	0.6	
Nausea	4.4	2.9	2.3	
Diarrhea	3.3	8.2	2.3	
Flatulence	3.3	1.8	0.6	
Viral infection	3.3	1.8	1.2	
Rhinitis	2.8	2.9	0.6	
Headache	2.2	2.9	2.9	
Coughing	1.7	2.9	2.9	
Injury accidental	1.7	2.9	1.2	
Any event causing withdrawal	6.1	9.9	7.0	
Any serious adverse event	0	1.2	1.7	

* All entries are % of patients.

Results in Period 2 were consistent with Period 1. Four patients experienced serious adverse events in Period 2: a case of cholecystitis in the celecoxib/acetaminophen sequence group; a case of increases in SGOT and SGPT in the acetaminophen/placebo sequence group; a case of neuropathy in the acetaminophen/celecoxib sequence group; and a case of intestinal obstruction in the acetaminophen/celecoxib sequence group.

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:

- Celecoxib was shown to be 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 only sporadically found to be statistically significant.
- When asked to compare the two regimens, patients who had received both celecoxib and acetaminophen strongly preferred celecoxib over acetaminophen. The separation between acetaminophen and placebo in this measure was not statistically significant.
- The three pairwise tests on the results in Period 1 showed that only celecoxib was significantly better than placebo statistically, by comparing treatments received by different patients. In contrast, the pairwise tests from Periods 1 and 2 combined, comparing treatments received by the same patient, showed celecoxib to be statistically significantly superior to both placebo and acetaminophen.

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 incidences were lowest for celecoxib, but the differences were small and not statistically significant.
- 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. The highest proportion of events rated as severe occurred in the placebo group.
- 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, and neither active treatment group had a higher incidence of serious adverse events than the placebo group.

Based on report completed: 20 May 2003