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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: Study I49-00-07-849

Supplement To Final Reports For Three Multi-Centre, Double-Blind, Parallel Group Studies Comparing The Efficacy And Incidence Of Gastroduodenal Ulcer Associated With SC-58635 (Celecoxib) 100 mg BID With That Of Diclofenac 50 mg BID Taken For 12 Weeks In Patients With Osteoarthritis Or Rheumatoid Arthritis in the People's Republic of China, Taiwan and Hong Kong

Study centre(s): People's Republic of China (Protocol I49-98-02-105): 14 study centers; Taiwan (Protocol I49-98-02-106): 6 study centers; Hong Kong (Protocol I49-98-02-107): 4 study centers

Publication (reference, if applicable) See attached bibliography

Studied period:	**Phase of development:**
People's Republic of China: 24 July 1999 to 26 April 2000 Taiwan: 22 April 1999 to 29 December 1999 Hong Kong: 02 August 1999 to 28 April 2000	Phase 3

Objectives:

Reported here:

- Compare the incidence of gastroduodenal ulcer over 12 weeks associated with SC-58635 100 mg BID with that of diclofenac 50 mg BID in patients with OA and RA combined.

Reported elsewhere:

- Compare the arthritis efficacy of SC-58635 100 mg BID with that of diclofenac 50 mg BID in patients with OA or RA.
- Compare the safety and tolerability of SC-58635 100 mg BID with that of diclofenac 50 mg BID in patients with OA or RA.

(These results are reported in the study reports of Protocol #I49-98-02-105 (China); Protocol #I49-98-02-106 (Taiwan); and Protocol #I49-98-02-107 (Hong Kong)).

Methodology: These were three double-blind, randomized, multicenter, active comparator (diclofenac) controlled, parallel group studies comparing the efficacy and incidence of gastroduodenal ulcer in OA or RA patients receiving SC-56835 (celecoxib) with those receiving diclofenac. The studies took place in the People's Republic of China (Protocol #I49-98-02-105), Taiwan (Protocol #I49-98-02-106) and Hong Kong

(Protocol #I49-98-02-107), respectively, and had identical design. Patients were randomly assigned to receive either SC-58635 100 mg BID or diclofenac 50 mg BID. Those patients who received SC-58635 100 mg also received diclofenac matched placebo and those patients who received diclofenac 50 mg also received SC-58635 matched placebo to maintain the double-blind study design (double-dummy design). The duration of treatment was 12 weeks, with visits occurring at screening/baseline, Weeks 4, 8 and 12. Scheduled endoscopies were performed prior to and 12 weeks after the first dose of study medication (or at early termination).

Number of patients (planned and analyzed): A total of 880 patients were enrolled and randomized in the three studies (SC-58635: 440 patients; Diclofenac: 440 patients) to receive double-blind study medication. One hundred and twenty-one of the 880 randomized patients were withdrawn during the course of the study, with 759 patients completing the study. Seven hundred and thirty-eight patients were female and 142 patients were male. The mean age was 50.9 years for the SC-58635 treatment group (range: 17 to 84 years) and 49.9 years for the diclofenac treatment group (range: 18 to 88 years) (individual results for the three studies are reported in the study reports of Protocol #I49-98-02-105 (China); Protocol #I49-98-02-106 (Taiwan); and Protocol #I49-98-02-107 (Hong Kong)). Eight hundred and sixty-nine patients (SC-58635: 434 patients; Diclofenac: 435 patients) were included in the safety population and the intent-to-treat (ITT) population.

Diagnosis and main criteria for inclusion: Patients were included in the studies if they had a documented clinical diagnosis of OA or RA with a Functional Capacity Classification of I-III, required chronic nonsteroidal anti-inflammatory drugs (NSAIDs), and met the inclusion/exclusion criteria.

Duration of treatment: The treatment period was defined as the 12-week interval during which study medication was taken. The Week 4, 8 and 12 visits occurred during this interval. The Week 4 visit had to occur 28 days (± 5 days), the Week 8 visit 56 days (± 5 days), and the Week 12 visit 84 days (± 5 days) after the date of the first dose of medication.

Test product, dose and mode of administration: Celecoxib (SC-58635) 100 mg capsules, one capsule orally BID; and placebo, one capsule orally BID.

Reference therapy, dose and mode of administration: Diclofenac 50 mg film-coated tablets, one tablet orally BID; and placebo, one tablet orally BID.

Criteria for evaluation:

Criteria for evaluation of arthritis efficacy and safety are described in the study reports of Protocol #I49-98-02-105 (China); Protocol #I49-98-02-106 (Taiwan); and Protocol #I49-98-02-107 (Hong Kong).

Endoscopy:
Gastroduodenal scores, gastric scores and duodenal scores were assigned using the following scale:

Score:
- 0 - No visible lesions (i.e., normal mucosa)
- 1 - 1-10 Petechiae
- 2 - >10 Petechiae
- 3 - 1-5 Erosions
- 4 - 6-10 Erosions
- 5 - 11-25 Erosions
- 6 - >25 Erosions
- 7 - Ulcer

The gastroduodenal score is the maximum of the gastric and/or duodenal scores. Gastric, duodenal and gastroduodenal ulcer rate (score = 7) and ulcer/erosion rate (score>=3) at the final visit were calculated. Time to first ulcer was also assessed.

Statistical methods: All analyses were applied to the intent-to-treat patient population. The statistical methods for the evaluation of arthritis efficacy and safety data are described in the study reports of Protocol #I49-98-02-105 (China); Protocol #I49-98-02-106 (Taiwan); and Protocol #I49-98-02-107 (Hong Kong).

Endoscopy: As stipulated in the original protocols, the endoscopy data of the three companion studies (Protocol #I49-98-02-105 (People's Republic Of China), Protocol #I49-98-02-106 (Taiwan) and Protocol #I49-

98-02-107 (Hong Kong)) were pooled for analysis. The primary endoscopy variable was the cumulative incidence of gastroduodenal ulcers over 12 weeks of treatment.

Gastric, duodenal and gastroduodenal ulcer rates (score = 7) and ulcer/erosion rates (score >=3) at the final visit were analyzed using Cochran-Mantel-Haenszel (CMH) tests stratifying by baseline status. Time to ulcer was analyzed by survival analysis techniques. Risk factors for ulcers were investigated as appropriate.

Gastric scores, duodenal scores and gastroduodenal scores at Final visit were analyzed using a two-way analysis of covariance (ANCOVA) with investigational site and treatment as factors and the baseline score as a covariate.

SUMMARY – CONCLUSIONS

DEMOGRAPHY:

The study was well balanced between treatment groups in terms of patient baseline characteristics (demography, arthritis assessments and endoscopy scores). Of the 880 patients, 738 were female and 142 male. The race/ethnic origin of all patients was Asian, except for two patients who were documented as White and Black, respectively. The mean age of the patients was 50.9 years for the SC-58635 treatment group (range: 17 to 84 years) and 49.9 years for the diclofenac treatment group (range: 18 to 88 years).

EFFICACY RESULTS:

The details of the efficacy results are reported in the study reports of Protocol #I49-98-02-105 (China); Protocol #I49-98-02-106 (Taiwan); and Protocol #I49-98-02-107 (Hong Kong).

SAFETY RESULTS

The details of the safety results are reported in the study reports of Protocol #I49-98-02-105 (China); Protocol #I49-98-02-106 (Taiwan); and Protocol #I49-98-02-107 (Hong Kong).

ENDOSCOPY RESULTS

UGI Endoscopy Final Crude Ulcer Rate

	SC-58635 100 mg BID (N= 434)	**Diclofenac 50 mg BID (N= 435)**	**p-value(a)**
Cumulative Gastroduodenal Ulcers	2.8% (11/398)	5.1% (20/390)	0.083
Cumulative Gastric Ulcers	0.5% (2/398)	3.6% (14/390)	0.002
Cumulative Duodenal Ulcers	2.3% (9/398)	1.5% (6/390)	0.452

(a) Cochran-Mantel-Haenszel test of overall comparison stratified by baseline status (p-value from Row Mean Scores Differ)

Evaluation of the UGI safety results over the 12 weeks of the study showed that SC-58635, at the doses of 100 mg BID is generally associated with lower rates of gastroduodenal ulcers and significantly lower gastric ulcer rate than diclofenac at the dose of 50 mg BID. Ulceration of the gastroduodenal mucosa was observed in 11 (2.8%) patients in the SC-58635 100 mg BID group whereas in the diclofenac 50 mg BID group showed 82% higher ulceration rate, 20 (5.1%) patients. The rate of gastroduodenal ulcers on SC-58635 was consistent with prior endoscopy studies conducted in other regions and corresponds with placebo rates observed in prior controlled studies.

Compared to prior UGI endoscopy studies, this study included a group of OA/RA patients with very few NSAID risk factors (low mean age, low percentage of history of gastroduodenal ulcers, GI bleeding and cardiovascular disease). As would be expected given this population, gastroduodenal ulcer rates for the cohort were very low. Furthermore, the rate of gastroduodenal ulcers for diclofenac was much lower than historical data, but was consistent with the low risk patient population.

Risk factor analysis for gastroduodenal ulcers confirms the effect of age on ulcer rates. The trend towards a gender effect is consistent with other studies but may be a result of the association of sex with other co-morbidities such as cardiovascular disease. Other risk factors were too infrequent to yield reliable results. In summary, the study results suggest that SC-58635 100 mg BID is associated with a lower rate of endoscopic gastroduodenal ulcers than diclofenac 50 mg BID in a Chinese population although the low risk patient population reduced the difference between SC-58635 and the comparator NSAID, diclofenac.

Based on a Report Completed: 01 August 2000