CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20998/S007

CORRESPONDENCE

OCT - 7 1999

NDA 21-156

G. D. Searle & Co.
Attention: Anita Piergiovanni, M.Sc.
Director, Worldwide Regulatory Affairs
4901 Searle Parkway
Skokie, IL 60077

Dear Ms. Piergiovanni:

Reference is made to your correspondence dated August 26, 1999, requesting a waiver for pediatric studies under 21 CFR 314.55(c).

We have reviewed the information you have submitted and agree that a waiver is justified for Celebrex™ (celecoxib) for the regression and prevention of adenomatous colorectal polyps in patients with familial adenomatous polyposis for the pediatric population.

Accordingly, a waiver for pediatric studies for this application is granted under 21 CFR 314.55 at this time.

If you have questions, please contact Paul Zimmerman, Regulatory Project Manager, at (301) 594-5775.

Sincerely,

/S/ MD
10-7-99

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

SEARLE

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077

December 23, 1999

Richard Pazdur M.D., Director
Center for Drug Evaluation and Research
Division of Oncologic Drug Products, HFD 150
1451 Rockville Pike
Rockville, MD 20852-1420

RE: NDA 21-156
CELEBREX™ (celecoxib)
Familial Adenomatous Polyposis (FAP)
Final FAP Labeling (Package Insert)

Dear Dr. Pazdur:

Reference is made to NDA 21-156 for CELEBREX (celecoxib) for use in Familial Adenomatous Polyposis (FAP) submitted by Searle on June 24,1999. CELEBREX™ is a nonsteroidal anti-inflammatory drug which inhibits cyclooxygenase-2 (COX-2), but at therapeutic concentrations in humans, does not inhibit cyclooxygenase-1 (COX-1). It is currently approved for the relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis in adults.

Reference is made to discussions at our teleconference with the agency on December 22 and the fax of December 22 regarding Phase 4 requirements and commitments from Paul Zimmerman, Project Manager in your Division. We herein submit the agreed-upon package insert to NDA #21-156. Also, as advised by Paul Zimmerman and in accordance with 21 CFR 314.70(b), we are submitting this revised package insert with the FAP-related wording and the other revisions discussed with the Division of Anti-Inflammatory, Analgesic and Opthalmic Drug Products as a labeling Supplement (#007) to NDA #20-998 (arthritis).

<u>The following are agreed to as phase 4 commitments for CELEBREX—NDA 21-156 (from the above-referenced fax dated December 22, 1999):</u>

I. Phase 4 commitments that are required for accelerated approval

   A. A randomized controlled trial in familial adenomatous polyposis (FAP) that will verify and describe the clinical benefit of Celebrex in this population, as required under Subpart H regulations (21 CFR 314.510). Our proposal for a placebo-controlled study of adolescents with FAP aged 12 to 19 years who are genotypically positive but phenotypically negative is acceptable to FDA, pending agreement on design issues noted in Paul Zimmerman's fax of December 22, 1999. This study will be completed and results submitted to FDA with due diligence.

B. A long-term registry of clinical outcomes in FAP patients. Our proposal for enrolling patients aged 12 years or above to Celebrex 400 mg BID is acceptable to FDA. Eligible patients would include those who are phenotypically positive who: 1) have not had primary prophylactic surgery; 2) have not had secondary surgery, or; 3) have had both primary and secondary surgery. Time to FAP-related events (FAP-related surgery, gastrointestinal cancer, desmoids, or death) and adverse events will be collected and compared to untreated historical controls. Information collected on registry patients will be submitted to the NDA on an annual basis.

II. Additional phase 4 commitments that are not a condition of the accelerated approval

A. A randomized controlled trial in sporadic adenomatous polyps. Our proposal for a placebo-controlled study evaluating the proportion of patients with new adenomas at year 1 and year 3 is generally acceptable to FDA. This study is being conducted under NCI IND .

B. For patients on Study 001, submission of data on the number of polypectomies performed, the size and histology of polyps removed, including diagnosis of malignancy, for each treatment arm. Correlation of polypectomy findings with the observed reduction in polyp counts will be made for each arm. Searle will provide a timeframe for submission of this data.

C. For patients on Study 001, submission of biomarker data for each treatment arm (e.g., crypt morphology and apoptotic index, p53 expression, COX messenger RNA/protein expression, etc.). Correlation of biomarker findings with the observed reduction in polyp counts will be made for each arm. Searle will provide a timeframe for submission of this data.

D. For patients on Study 001, submission of data on dietary habits at baseline and on study, for each treatment arm. If imbalances across arms are noted, an analysis of the impact of dietary factors on polyp reduction should be performed. Searle will provide a timeframe for submission of this data.

We understand that both NDA 21-156 and the labeling supplement to NDA #20-998 (arthritis) are submitted for approval by the Division of Oncologic Drug Products.

Should you require clarification or additional information, please contact the undersigned.

Sincerely yours,

Anita Piergiovanni

Anita Piergiovanni, M.Sc.
Director of Worldwide Regulatory Affairs
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

Chemoprevention Branch
Division of Cancer Prevention
EPN 201
6130 Executive Blvd.
Rockville, MD 20852
Phone 301-496-8563
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February 8, 1999

Robert L. Justice, MD, Director
Division of Oncologic Drug Products, HFD 150
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

Subject: Celecoxib (SC-58635) IND Debarment Certification

Dear Dr. Justice:

NCI, Division of Cancer Prevention (DCP) sponsored development of celecoxib under NCI IND Pursuant to section 306 (k) of the Federal Food, Drug and Cosmetic Act, NCI, DCP certifies that it did not and will not use in any capacity the services of any person disbarred under subsection (a) or (b), in connection with the supplemental NDA.

Sincerely,

Gary J. Kelloff, MD
Chief, Chemoprevention Branch
Division of Cancer Prevention, NCI

Ernest Hawk, MD
Medical Monitor, Chemoprevention Branch
Division of Cancer Prevention, NCI