FINDING OF NO SIGNIFICANT IMPACT

NDA 20-998

Celecoxib Capsules

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement, therefore, will not be prepared.

In support of their new drug application for Celecoxib Capsules, G.D. Searle & Co. has prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts of the use and disposal from use of the product. Celecoxib is a chemically synthesized drug which is intended for the management of pain and for the acute and long-term treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis.

Celecoxib may enter both the aquatic and terrestrial environment from patient use and disposal. Although degradation mechanisms have been demonstrated for the aquatic and terrestrial environment, they are slow. As the drug is expected to persist in the environment for some time, the toxicity of celecoxib to environmental organisms was characterized. The results indicate that the compound is not expected to be toxic to organisms at the expected environmental introduction concentration.

At U.S. hospitals and clinics, empty or partially empty packages will be disposed of according to hospital/clinic procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.
PREPARED BY
Nancy B. Sager
Environmental Officer
Center for Drug Evaluation and Research

CONCURRED
Eric B. Sheinin, Ph.D.
Director, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Attachment: Environmental Assessment
APPENDICES

Appendix 1.
Appendix 1.1  Citation of and Statement of Compliance with Applicable Emission Requirements
April 15, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
(HFD-357)
5600 Fishers Lane
Rockville, Maryland 20857

Re: COMPLIANCE WITH ENVIRONMENTAL AND OCCUPATIONAL REGULATIONS

SEARLE

Dear Sirs:

This letter certifies that Searle, located at:

99 Jardines Street
Caguas, Puerto Rico 00725

is in full compliance with all air, solid waste, hazardous waste and waste water permits. This letter also certifies that Searle is in complete compliance with all required occupational regulations governing the safety of its workforce.

The proposed manufacture of the SC-58635 drug product is not expected to cause environmental permits to be violated nor cause plant safety to be compromised. The current programs implementing good environmental management practices, policies and procedures will remain in effect.

Sincerely,

[Signature]
Daniel Lebrón
President & General Manager
April 16, 1998

Food and Drug Administration
Center for Drug Evaluation and Research (HFD-357)
5600 Fishers Lane
Rockville, Maryland 20857

Re: Compliance Certification for Manufacture of Drug Substance

\textit{SEARLE}

Dear Sirs:

This letter certifies that Searle, located at 1750 Lovers Lane in Augusta, Georgia, is in full compliance with federal, state, and local air, wastewater, solid and hazardous waste environmental regulations and permit conditions.

I also certify that Searle is in complete compliance with all occupational regulations governing the safety of the workforce responsible for the manufacturing, handling, and packaging of the drug substance.

Approval for the manufacture of the celecoxib drug substance will not cause an environmental permit violation to occur at the facility, nor will plant safety be compromised. The environmental management practices, policies, and procedures currently in place at the Searle manufacturing site will remain in effect.

Sincerely,

William DeFer
Site Manager
Appendix 1.2    MSDS for SC-58635
MATERIAL SAFETY DATA SHEET

SECTION 1  CHEMICAL PRODUCTS & COMPANY IDENTIFICATION

2. SEARLE

3. BOX 5110

4. CHICAGO, IL 60680

5. 58635

6. CAS Number: 169590-42-5

7. RTECS: Not Assigned

3STANCE: Celecoxib

8. IDE NAMES/SYNONYMS: 4-[(5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-razol-1-yl)benzenesulfonamide; SC58635

CREATION DATE: 5/17/94  REVISION DATE: 11/3/97

SECTION 2  COMPOSITION/INFORMATION ON INGREDIENTS

9. COMPONENT  CAS NUMBER  PERCENTAGE  EXPOSURE GUIDELINES

10. 58635  169590-42-5  100  Not established

SECTION 3  HAZARDS IDENTIFICATION

11. RATINGS (Scale 0-4): Health=2  Fire=1  Reactivity=1

(U=Unknown)

EMERGENCY OVERVIEW:
Celecoxib is a white solid material developed as an anti-inflammatory drug. The toxicological, physical and other potential hazards associated with this chemical have not been fully characterized. Care should be exercised in handling.

ENTIAL HEALTH EFFECTS:

12. INHALATION:
SHORT TERM EXPOSURE: No information regarding inhalation hazards
LONG TERM EFFECTS: No information regarding inhalation hazards

13. IN CONTACT:
SHORT TERM EXPOSURE: No information regarding skin irritation
LONG TERM EFFECTS: No information regarding skin contact

14. ON CONTACT:
SHORT TERM EXPOSURE: May cause irritation
LONG TERM EFFECTS: See Short Term Exposure
SHORT TERM EXPOSURE:
Based on early studies, it appears that the predominant adverse effects of clinical use of this drug are: flu-like symptoms, headache, fever, chills, fatigue, joint and muscle aches, flushing, cardiac arrhythmias, supraventricular tachycardia, congestive heart failure and platelet count decreases.

LONG TERM EFFECTS: No information regarding ingestion hazards

CINOGEN STATUS: No information available

SECTION 4 FIRST AID MEASURES

ALERTION:
Remove to fresh air, monitor blood pressure, respiration, temperature and general condition. Get medical attention promptly.

IN CONTACT:
Remove contaminated clothing. Wash skin with soap and water. Get medical attention if irritation develops.

CONTACT:
Immediately flush eyes with large amounts of water for 15 minutes. Get medical attention promptly.

REASON:
Provide general support and monitor blood pressure, respiration, temperature and general condition. Get medical attention promptly.

TO PHYSICIAN: See Section 11
IDOTE: No antidote appropriate. Supportive care as indicated.

SECTION 5 FIRE FIGHTING MEASURES

AND EXPLOSION HAZARD: Will burn if involved in a fire

AH POINT: Not applicable

ER FLAMMABLE LIMIT: Not applicable

ER FLAMMABLE LIMIT: Not applicable

IGNITION: Not applicable

MABILITY CLASS (OSHA): Not known

ARDOUS COMBUSTION PRODUCTS:
Hydrogen fluoride, oxides of nitrogen and sulfur

INGUISHING MEDIA:
Use dry chemical, carbon dioxide, water spray, regular foam or extinguishing agent suitable for surrounding fire.
EFIGHTING:
Evacuate area and fight fire from a safe distance. As in any fire, ear pressure demand self-contained breathing apparatus, and full protective gear.

SECTION 6  ACCIDENTAL RELEASE MEASURES

UPATIONAL SPILL:
Vacuum material with HEPA filtered vacuum cleaner or wet sweep. Collect waste for proper disposal. Keep unnecessary people away. Do not flush spilled material into sewer.

SECTION 7  HANDLING AND STORAGE

with adequate ventilation. Avoid breathing dust. Avoid contact with skin, skin or clothing. No special storage provisions necessary.

SECTION 8  EXPOSURE CONTROLS/PERSONAL PROTECTION

SUREMENT METHOD: Not established

ATION: Local exhaust ventilation

PROTECTION: Safety glasses

THING: Long sleeves (if potential for skin contact) and disposable coveralls.

VES:
Chemically resistant gloves should be used. This compound has not been specifically evaluated for glove suitability.

IRATORY PROTECTION:
Choice of respirators can vary depending on individual circumstances. The specific application should be evaluated to determine if the following recommendations are appropriate.

HEPA air-purifying respirator for operations with adequate ventilation but with some potential for exposure (such as manual transfer operations).

Supplied-air respirator for operations without adequate ventilation.

FIREFIGHTING AND OTHER IMMEDIATELY DANGEROUS TO LIFE OR HEALTH DITIONS WEAR: Self-contained breathing apparatus

SECTION 9  PHYSICAL AND CHEMICAL PROPERTIES
DESCRIPTION: White solid

Molecular Weight: 381.38

Molar Formula: C17H14F3N3O2S

Melting Point: Not applicable

Boiling Point: 156-157°C

Flash Point: Not applicable

Specific Gravity: Not known

Dissolution: Not soluble in water

Latent Heat: Not applicable

Boiling Point: Not known

Evaporation Rate: Not applicable

Density: Not applicable

Vent Solubility: Acetone, ethanol, DMSO, ethyl acetate and methylene chloride

Not applicable

SECTION 10 STABILITY AND REACTIVITY

Stability: Stable under normal conditions of temperature and pressure.

Conditions to Avoid: Not known

Stability: Not known

Hazardous Decomposition: Hydrogen fluoride, oxides of nitrogen and sulfur

Hazard: Not known

SECTION 11 TOXICOLOGY INFORMATION

Toxicity: Minimal irritant in rabbits

Inhalation: Non-irritating in rabbits

Toxicity Data:
- Rat—Oral LD50: > 2000 mg/kg
- Dog—Oral LD50: > 2000 mg/kg


Carcinogenicity: Not known

Genotoxic Effects: A NOEL of 20 mg/kg/day was reported in a six (6) month study in rats.
CHRONIC EFFECTS:
Gastrointestinal injury (300 mg/kg/day and higher) and renal effects (1000 mg/kg/day) have been observed in mice in a 2 week dietary study. The no-observed-effect-level (NOEL) was 100 mg/kg/day in males and 300 mg/kg/day in females.

A NOEL of 20 mg/kg/day was reported in a 13 week oral dose study in rats.

In a 4 week oral dog study, mortality/moribundity was seen at doses of 100 mg/kg/day and higher. A NOEL of 35 mg/kg/day was reported in a 13 week oral dose study in dogs. Gastrointestinal injury and renal effects were noted at doses of 50 mg/kg/day and higher. The NOEL dose was 25 mg/kg/day. These target organ effects are consistent with those reported for NSAIDS.

PRODUCTIVE:
Evidence of embryotoxicity was observed at exposures greater than ten times the projected efficacious exposure. This effect is consistent with effects reported for non-steroidal anti-inflammatory drugs (NSAIDS).

IMMUNOGENICITY:
No evidence of malformations produced by SC-58635 was observed in studies in rats and rabbits.

ALLERGIC EFFECTS:
Negative for antigenicity in studies with mice and guinea pigs. Negative in a guinea pig maximization study for dermal sensitization.

Dermal Effects:
Gastrointestinal tract and kidney.

INCREASED RISK FROM EXPOSURE: Not known

ADDITIONAL DATA: None

SECTION 12 ECOLOGICAL INFORMATION

ENVIRONMENTAL OVERVIEW:
The environmental and ecological aspects of this chemical have not been fully characterized. Care should be used in handling.

AQUATIC TOXICITY: Not known

HABITABILITY: Not known

BIOCONCENTRATION FACTOR (BCF): Not known

OCTANOL/WATER PARTITION COEFFICIENT: Not known

DISPOSAL INFORMATION
(●) Inert in approved facility. Observe all federal, state and local regulations when disposing of this substance.

SECTION 14 TRANSPORTATION INFORMATION

HAZARDOUS MATERIALS DESCRIPTION/PROPER SHIPPING NAME: IATA (air): Other regulated substance, 9, ID 8027; DOT (ground): Not regulated

HAZARD CLASS: 9

IDENTIFICATION NUMBER: ID 8027

SECTION 15 REGULATORY INFORMATION

NECS NUMBER: Not assigned

TA STATUS: Not applicable

RCLA SECTION 103 (40CFR302.4): Not applicable

TA SECTION 302 (40CFR355.30): Not applicable

TA SECTION 304 (40CFR355.40): Not applicable

TA SECTION 313 (40CFR372.65): Not applicable

TA PROCESS SAFETY (29CFR1910.119): Not applicable

CALIFORNIA PROPOSITION 65: Not applicable

TA: Not applicable

HAZARD CATEGORIES, SARA SECTIONS 311/312 (40 CFR 370.21)

TE HAZARD: Not applicable

RASONIC HAZARD: Not applicable

E HAZARD: Not applicable

ACTIVITY HAZARD: Not applicable

DEN RELEASE HAZARD: Not applicable

Information here provided is believed to be accurate and represents the best information currently available to Searle, and Searle assumes no liability resulting from its use. Users should make their own investigations to determine the suitability of the information for their particular purposes.