CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-776

PHARMACOLOGY REVIEW(S)

Date: 19-May-1998
From: Almon W. Coulter

To: Christina Fang, M.D.
Subject: NDA 20-776
Labeling for

Carcinogenesis, mutagenesis, impairment of fertility: In oncogenicity studies, oxaprozin administration for 2 years was associated with the exacerbation of liver neoplasms (hepatic adenomas and carcinomas) in male CD mice, but not in female CD mice or rats. The significance of this species-specific finding to humans is unknown.
Oxaprozin did not display mutagenic potential. No evidence of genetic toxicity or cell-transforming ability was found in test results from the Ames test, forward mutation in yeast and Chinese hamster ovary (CHO) cells, DNA repair testing in CHO cells, micronucleus testing in mouse bone marrow, chromosomal aberration testing in human lymphocytes, or cell transformation testing in mouse fibroblasts.
Oxaprozin administration was not associated with impairment of fertility in male and female rats at oral doses up to 200 mg/kg/day (1180 mg/m^2/day); the usual human dose is 17 mg/kg/day (629 mg/m^2/day). However, testicular degeneration was observed in beagle dogs treated with 37.5 to 150 mg/kg/day (750 to 3000 mg/m^2/day) of oxaprozin for 6 months, or 37.5 mg/kg/day for 42 days, a finding not confirmed in other species. The clinical relevance of this finding is not known.
Pregnancy: Teratogenic Effects-Pregnancy Category C.
There are no adequate or well-controlled studies in pregnant women. Teratology studies with oxaprozin were performed in mice, rats, and rabbits. In mice and rats, no drug-related developmental abnormalities were observed at 50 to 200 mg/kg/day of oxaprozin (225 to 900 mg/m^2/day). However, in rabbits, infrequent malformed fetuses were observed in dams treated with 7.5 to 30 mg/kg/day of oxaprozin (the usual human dosage range). Oxaprozin should be used during pregnancy only if the potential benefits justify the potential risks to the fetus.
Nonteratogenic effects
Because of the known effects on nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.
Labor and delivery
In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of on labor and delivery in pregnant women are unknown.
Nursing mothers
Studies of oxaprozin excretion in human milk have not been conducted; however, oxaprozin was found in the milk of lactating rats. Since the effects of oxaprozin on infants are not known and since there is a potential for serious adverse reactions in nursing infants, caution should be exercised if oxaprozin is administered to nursing women.

Will Coulter

NDA 20-776

cc:

NDA
DivFile
HFD-550 JE Hyde/C Fang/ W Coulter/V Lutwak

HFD 550/Lot wrk

JUN 26 1997

THE DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG PRODUCTS

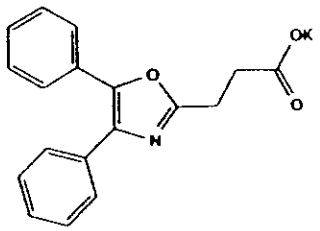
PHARMACOLOGY - TOXICOLOGY REVIEW
INITIAL REVIEW

NDA 20-776

SPONSOR:	G. D. Searle & Co. 4901 Searle Parkway Skokie, Illinois 60077
DRUG:	— (oxaprozin potassium), 600 mg tablet
SUBMISSION:	May 19, 1997
DATE RECEIVED:	May 20, 1997
REVIEW COMPLETED:	June 6, 1997
REVIEWER:	Almon W. Coulter, Ph.D.

DRUG CATEGORY:	NSAID
RELATED INDs/NDAs:	— IND 33,501 oxaprozin - Dapro (G.D. Searle & Co.) IND 47,340 oxaprozin potassium (G.D. Searle & Co.) NDA 18-841 oxaprozin - Daypro (Searle), approved on October 29, 1992.
PROPOSED INDICATION:	— is indicated for the —
the	relief of the signs and symptoms of OA and RA.
DOSAGE AND ADMINISTRATION:	OA: 1200 mg (two 600 mg caplets) once a day RA: 1200 mg (two 600 mg caplets) once a day

DRUG SUBSTANCE:



Chemical Names: 4,5-Diphenyl-2-oxazolepropanoic acid, potassium salt
N-(2-oxo-1,2-diphenylethyl)-succinamic acid, potassium salt

Generic Name: Oxaprozin Potassium

Code Name: SC-62845

CAS Registry Nº: CAS-174064-08-5

Formula: $C_{18}H_{14}KNO_3$

Molecular Weight: 331.40

Appearance: White to off white powder.

Solubility: — in water at 25°C

FORMULATION:

—	mg/tablet	—	mg/tablet
Oxaprozin Potassium	—	— Blue	—
Microcrystalline Cellulose NF	—	—	
Pregelatinized Corn Starch NF	—	—	
Stearic Acid NF	—	—	
Colloidal Silicon Dioxide NF		—	
—	—		

[1] Equivalent to 600 mg oxaprozin
[2] Adjustment of the composition was made to accommodate —

PRECLINICAL STUDIES:

In a meeting held on December 16, 1994 between Searle and the Pilot Drug Evaluation

RECOMMENDATIONS

There are no objections to the approval of this application, based on the preclinical pharmacology-toxicology.

Almon W Coulter
Almon W. Coulter, Ph.D.

Conrad H. Chen 6-26-97
Team Leader: Conrad Chen, Ph.D.

cc:
NDA 20-776
HFD-550/Division File
/ACoulter
/CFang
/CYaciw
/VLutwak
F/T by AWC: June 6, 1997