CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-547/S007

PHARMACOLOGY REVIEW(S)

DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Label Review

NDA 20-547-S007

Date of Submission: 9/18/98

Information to be Conveyed to Sponsor: Yes (X), No ( )

Reviewer: Lawrence F. Sancilio, Ph.D.

Date Review Completed: 9/16/99

Sponsor: Zeneca Pharmaceuticals
1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-2125

Drug Name: Zafirlukast (Accolate), ICI 204,219

Chemical Name: N- [4- (5-(cyclopentyloxycarbonyl) amino-1-methylindol-3-ylmethyl]-3-methoxybenzoyl]-2-methylbenzenesulfonamide

Class: Antagonist of LTC_4, LTD_4 and LTE_4

Indication: Prophylaxis and chronic treatment of asthma in pediatric patients, 7-11 years of age.

Formulation: Tablets containing 10 and 20 mg of zafirlukast.

Maximum Daily Oral Dose: Adults: 40 mg, 0.8 mg/kg, 29.6 mg/m^2.
Children, 7-11 years old: 20 mg, 0.8 mg/kg, 20 mg/m^2

Route of Administration: Oral

Summary and Evaluation

This supplement of NDA 20-547 is for the prophylaxis and chronic treatment of asthma in pediatric patients, 7-11 years of age. The maximum daily oral dose for children is 20 mg and 40 mg for adults. Zafirlukast has already been approved for this indication in adults. The Pharmacology and Toxicology of zafirlukast has been studied in depth (see the review of the pharmacologic and toxicologic studies submitted in the original NDA.)

The following table compares the pharmacokinetics of zafirlukast in animals and man.

Parameter	Species: Human	Rat	Mouse	Dog
Metabolic Profile	Metabolites found in humans were detected in the rat, mouse and dog.			
Protein Binding	99.7-99.9% in all species			
Metabolized	33%	4%	2%	5%

The ratios comparing the animal exposure with the adult and children exposure are shown in the following table.

Study/ Species/ Dose, mg/kg /Day/ Route	AUC, μg.h/ml	AUC, Animal / AUC, Adult	AUC Animal / AUC, Child
Carcinogenicity Study, Oral			
Mouse, 300, Diet	253[a]	74	83
100	136[b]	40	45
Rat, 2000, Diet	2150[c]	630	712
400	1865[c]	547	618
Developmental Toxicity			
Monkey, 2000, Oral	411[d]	121	
Adult, 0.8, Oral	3.41[e]		
Children, 7- 11 years old, 1.0, Oral	3.03[f]		

[a] Extrapolated from a 90-day dietary study (IND [redacted] review of Y.S. Choi, 2/25/91).
[b] IND [redacted] review of Y.S. Choi, 2/25/91.
[c] IND [redacted] review of C. J. Sun, 1/8/92; data determined by extrapolation or by regression analysis.
[d] NDA 20-547, review of L.F. Sancilio, 8/29/96.
[e] Two times the AUC $_{0\text{-}tau}$ determined from a 20 mg b.i.d. dosing schedule; the blood was withdrawn on day 5 following the morning 20 mg dose in a 10-day study (6/26/95, NDA 20547, vol. 1.2 p 178) and adjusted for 33% metabolism.
[f] AUC $_{0\text{-}inf}$ (9/17/98, NDA 20-547, S-007,vol. 50.7, p 6.F.2); the AUC was extrapolated to twice the AUC of a 10 mg dose and adjusted for 33% metabolism.

Label Review

The following sections were revised; deletions are indicated by ~~strikeout~~.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

In two-year carcinogenicity studies, zafirlukast was administered dietary doses of 10, 100 and 300 mg/kg to mice and dietary doses of 40, 400 and 2000 mg/kg to rats. Male mice given 300 mg/kg/day (approximately 75 times the maximum recommended daily oral dose in adults and in children based on comparison of the plasma area-under the curves [AUCs] values of total drug exposure) showed an increased incidence of hepatocellular adenomas [redacted] female mice at this dose showed a greater incidence of whole body histocytic sarcomas. Male and female rats given an oral dose of 2000 mg/kg/day (approximately 630 times the maximum recommended daily oral dose in adults and in children based on comparison of the AUCs of total drug exposure) of zafirlukast showed [redacted] an increased incidence of

urinary bladder transitional cell papillomas [redacted] Zafirlukast was not tumorigenic at oral doses up to 100 mg/kg (approximately 40 times the maximum recommended daily oral dose in adults and in children based on comparison of the AUCs of total drug exposure) in mice and at oral doses up to 400 mg/kg (approximately 550 times the maximum recommended daily oral dose in adults and in children based on comparison of the AUCs of total drug exposure). The clinical significance of these findings for the long-term use of **ACCOLATE** is unknown.

Zafirlukast showed no evidence of mutagenic potential in the reverse microbial assay, in 2 forward point mutation (CHO-HGPRT and mouse lymphoma) assays or in two assays for chromosomal aberrations (the in vitro human peripheral blood lymphocyte clastogenic assay and the [redacted] rat bone marrow micronucleus assay).

No evidence of impairment of fertility and reproduction was seen in male and female rats treated with zafirlukast at oral doses up to 2000 mg/kg (approximately 410 times the maximum recommended daily oral dose in adults on a mg/m^2 basis)

Pregnancy Category B: No teratogenicity was observed at oral doses up to 1600 mg/kg/day in mice (approximately 160 times the maximum recommended human oral daily dose on a mg/m^2 basis), 2000 mg/kg/day in rats (approximately 410 times the maximum recommended daily oral dose in adults on a mg/m^2 basis) and 2000 mg/kg/day in cynomolgus monkeys (approximately 120 times the maximum recommended daily oral dose in adults based on comparison of the AUCs of total drug exposure). At an oral dose of 2000 mg/kg/day in rats, maternal toxicity and deaths were seen with increased incidence of early fetal resorption. Spontaneous abortions occurred in cynomolgus monkeys at the maternally toxic dose of 2000 mg/kg/day. There are no adequate and well controlled trials in pregnant women. Because animal reproductive studies are not always predictive of human response, **ACCOLATE** should be used during pregnancy only if clearly needed.

Nursing Mothers

The information under this heading is acceptable and needs no changes.

OVERDOSAGE

No deaths occurred at oral zafirlukast doses of 2000 mg/kg in mice (approximately 200 times the maximum recommended daily oral dose in adults and approximately 300 times the maximum recommended daily oral dose children on a mg/m^2 basis), 2000 mg/kg in rats (approximately 410 times the maximum recommended daily oral dose in adults and approximately 600 times the maximum recommended daily oral dose children on a mg/m^2 basis) and 500 mg/kg in dogs (approximately 340 times the maximum recommended daily oral dose in adults and approximately 500 times the maximum recommended daily oral dose children on a mg/m^2 basis)

/S/ 9/14/99

Lawrence F. Sancilio, Ph.D.
Pharmacologist/Toxicologist

/S/ Sept. 16, 1999

cc. /Division File, NDA 20-547
/RAnthracite, HFD-570
/C.S.O., HFD-570
/LFSancilio, HFD-570

Approved by JSun

APPEARS THIS WAY
ON ORIGINAL

Drug: **Zafirlukast > 7 years**

	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m²
Pediatric		10	2	20	25	0.8000	25	20.00
Adult	>12	20	2	40	50	0.8000	37	29.60

	Route	mg/kg/d	conv. factor	mg/m²	Dose Ratio Adults	Dose Ratio Children	Rounded Dose Ratio Adults	Rounded Dose Ratio Children
Carcinogenicity:								
mouse			3	0	---	---	---	---
rat			6	0	---	---	---	---
hamster			4	0	---	---	---	---
rat			6	0	---	---	---	---
rat			6	0	---	---	---	---
Reproduction and Fertility:								
mouse			3	0	---	N/A	---	N/A
rat			6	0	---	N/A	---	N/A
rat			6	0	---	N/A	---	N/A
rat			6	0	---	N/A	---	N/A
Teratogenicity:								
mouse	p.o.	1600	3	4800	162.16	N/A	160	N/A
rat			6	0	---	N/A	---	N/A
rabbit			12	0	---	N/A	---	N/A
rabbit			12	0	---	N/A	---	N/A
extra			---	---	---	N/A	---	N/A
Overdosage:								
mouse	p.o.	2000	3	6000	202.70	300.00	200	300
mouse			3	0	---	---	---	---
rat	p.o.	2000	6	12000	405.41	600.00	410	600
rat			6	0	---	---	---	---
Other:	(Describe studies here)							
dog	p.o.	500	20	10000	337.84	500.00	340	500
dog			20	0	---	---	---	---
dog			20	0	---	---	---	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---