CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20547/S008

APPROVAL LETTER

MAR 17 1999

NDA 20-547/S-008

Zeneca Pharmaceuticals
1800 Concord Pike
P.O.Box 15437
Wilmington, Delaware 19850-5437

Attention: Mark A. DeSiato
Senior Regulatory Specialist
Marketed Products
Drug Regulatory Affairs Department

Dear Mr. DeSiato:

Please refer to your supplemental new drug application dated September 21, 1998, received September 22, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Accolate (zafirlukast) 20 mg Tablets.

We acknowledge receipt of your submissions dated January 20 and March 12, 1999.

This supplemental new drug application provides for changes to the Hepatic subsection of the PRECAUTIONS section and ADVERSE REACTIONS section. The language regarding elevation of liver enzymes and cases of symptomatic hepatitis and hyperbilirubinemia is revised. Agranulocytosis, bleeding, bruising and edema are added to the ADVERSE REACTIONS section.

We have completed the review of this supplemental application, as amended, and it is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on March 12, 1999.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-547/S-008." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Parinda Jani, Project Manager, at (301) 827-1064.

Sincerely yours,

John K. Jenkins, M.D., F.C.C.P
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20547/S008

FINAL PRINTED LABELING

Pharmacode supplied by IPR

670006

Rev H 03/99

APR 28 1999

PROFESSIONAL INFORMATION BROCHURE

ACCOLATE®

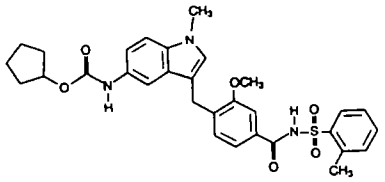
ZAFIRLUKAST

TABLETS

4-23-99

DESCRIPTION

Zafirlukast is a synthetic, selective peptide leukotriene receptor antagonist (LTRA), with the chemical name 4-(5-cyclopentyloxy-carbonylamino-1-methyl-indol-3-ylmethyl)-3-methoxy-N-o-tolylsulfonylbenzamide. The molecular weight of zafirlukast is 575.7 and the structural formula is:



The empirical formula is: $C_{31}H_{33}N_3O_6S$

Zafirlukast, a fine white to pale yellow amorphous powder, is practically insoluble in water. It is slightly soluble in methanol and freely soluble in tetrahydrofuran, dimethylsulfoxide, and acetone.

ACCOLATE is supplied as a 20 mg tablet for oral administration.

Inactive Ingredients: Film-coated tablets containing croscarmellose sodium, lactose, magnesium stearate, microcrystalline cellulose, povidone, hydroxypropylmethylcellulose and titanium dioxide.

CLINICAL PHARMACOLOGY

General: Zafirlukast is a selective and competitive receptor antagonist of leukotriene D_4 and E_4 (LTD_4 and LTE_4), components of slow-reacting substance of anaphylaxis (SRSA). Cysteinyl leukotriene production and receptor occupation have been correlated with the pathophysiology of asthma, including airway edema, smooth muscle constriction, and altered cellular activity associated with the inflammatory process, which contribute to the signs and symptoms of asthma. Patients with asthma were found in one study to be 25-100 times more sensitive to the bronchoconstricting activity of inhaled LTD_4 than nonasthmatic subjects.

In vitro studies demonstrated that zafirlukast antagonized the contractile activity of three leukotrienes (LTC_4, LTD_4 and LTE_4) in conducting airway smooth muscle from laboratory animals and humans. Zafirlukast prevented intradermal LTD_4-induced increases in cutaneous vascular permeability and inhibited inhaled LTD_4-induced influx of eosinophils into animal lungs. Inhalational challenge studies in sensitized sheep showed that zafirlukast suppressed the airway responses to antigen; this included both the early- and late-phase response and the nonspecific hyperresponsiveness.

In humans, zafirlukast inhibited bronchoconstriction caused by several kinds of inhalational challenges. Pretreatment with single oral doses of zafirlukast inhibited the bronchoconstriction caused by sulfur dioxide and cold air in patients with asthma. Pretreatment with single doses of zafirlukast attenuated the early- and late-phase reaction caused by inhalation of various antigens such as grass, cat dander, ragweed, and mixed antigens in patients with asthma. Zafirlukast also attenuated the increase in bronchial hyperresponsiveness to inhaled histamine that followed inhaled allergen challenge.

Clinical Pharmacokinetics and Bioavailability: Zafirlukast is rapidly absorbed following oral administration. The absolute bioavailability of zafirlukast is unknown. Peak plasma concentrations are achieved 3 hours after dosing.

The mean terminal elimination half-life of zafirlukast is approximately 10 hours in both normal subjects and patients with asthma. Steady-state plasma concentrations of zafirlukast are proportional to the dose and predictable from single-dose pharmacokinetic data.

Zafirlukast is extensively metabolized. Following oral administration of a radiolabeled dose, urinary excretion accounts for approximately 10% of the dose and the remainder is excreted in feces. Unmetabolized zafirlukast is not detected in urine. In vitro studies using human liver microsomes showed that the hydroxylated metabolites of zafirlukast are formed through the cytochrome P450 2C9 (CYP2C9) enzyme pathway. Additional in vitro studies utilizing human liver microsomes show that zafirlukast inhibits the cytochrome P450 CYP3A4 and CYP2C9 isoenzymes at concentrations close to the clinically achieved plasma concentrations. The metabolites of zafirlukast found in plasma are at least 90 times less potent as LTD_4 receptor antagonists than zafirlukast in a standard in vitro test of activity.

Cross-study comparisons in patients ranging from 7 years to greater than 65 years of age show that mean dose (mg/kg) normalized AUC and C_{max} increase and plasma clearance (CL) decreases with increasing age. In patients above 65 years of age, there is an approximately 2-3 fold greater C_{max} and AUC compared to young adult patients.

In a study of patients with hepatic impairment (biopsy-proven cirrhosis), there was a 50-60% greater C_{max} and AUC compared to normal subjects.

Based on a cross-study comparison, there are no apparent differences in the pharmacokinetics of zafirlukast between renally impaired patients and normal subjects.

In two separate studies, one using a high fat and the other a high protein meal, administration of ACCOLATE with food reduced the mean bioavailability by approximately 40%.

In the concentration range of 0.25-10 µg/mL, zafirlukast is >99% bound to plasma proteins, predominantly albumin.

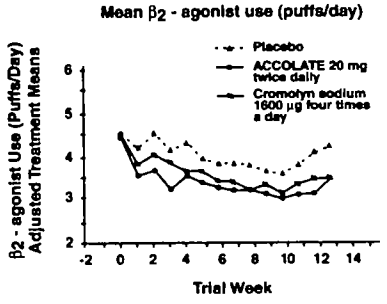
Clinical Studies: Three U.S. double-blind, randomized, placebo-controlled, 13-week clinical trials in 1,380 patients with mild-to-moderate asthma demonstrated that ACCOLATE improved daytime asthma symptoms, nighttime awakenings, mornings with asthma symptoms, rescue beta$_2$-agonist use, FEV_1, and morning peak expiratory flow rate. In these studies, the patients had a mean baseline FEV_1 of approximately 75% of predicted normal and a mean baseline beta-agonist requirement of approximately 4-5 puffs of albuterol per day. The results of the largest of the trials are shown in the table below.

Table 1
Mean Change from Baseline at Study Endpoint

	ACCOLATE 20 mg twice daily N=514	Placebo N=248
Daytime Asthma symptom score (0-3 scale)	-0.44*	-0.25
Nighttime Awakenings (number per week)	-1.27*	-0.43
Mornings with Asthma Symptoms (days per week)	-1.32*	-0.75
Rescue β_2-agonist use (puffs per day)	-1.15*	-0.24
FEV_1 (L)	+0.15*	+0.05
Morning PEFR (L/min)	+22.06*	+7.63
Evening PEFR (L/min)	+13.12	+10.14

*p<0.05, compared to placebo

In a second and smaller study, the effect of ACCOLATE on most efficacy parameters was comparable to the active control (inhaled cromolyn sodium 1600 µg four times per day) and superior to placebo at endpoint for decreasing rescue beta-agonist use (figure below).



In these trials, improvement in asthma symptoms occurred within one week of initiating treatment with ACCOLATE. The role of ACCOLATE in the management of patients with more severe asthma, patients receiving antiasthma therapy other than as-needed, inhaled beta$_2$-agonists, or as an oral or inhaled corticosteroid-sparing agent remains to be fully characterized.

INDICATIONS AND USAGE

ACCOLATE is indicated for the prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older.

CONTRAINDICATIONS

ACCOLATE is contraindicated in patients who are hypersensitive to zafirlukast or any of its inactive ingredients.

WARNINGS

ACCOLATE is not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus. Therapy with ACCOLATE can be continued during acute exacerbations of asthma.

Labeling: Div File
NDA No. 20547 Rcvd. 4-8-99
Reviewed by: 4-23-99

Coadministration of zafirlukast with warfarin results in a clinically significant increase in prothrombin time (PT). Patients on oral warfarin anticoagulant therapy and ACCOLATE should have their prothrombin times monitored closely and anticoagulant dose adjusted accordingly. (See PRECAUTIONS, Drug Interactions.)

PRECAUTIONS

Information for Patients: ACCOLATE is indicated for the chronic treatment of asthma and should be taken regularly as prescribed, even during symptom-free periods. ACCOLATE is not a bronchodilator and should not be used to treat acute episodes of asthma. Patients receiving ACCOLATE should be instructed not to decrease the dose or stop taking any other antiasthma medications unless instructed by a physician. Women who are breast-feeding should be instructed not to take ACCOLATE (see PRECAUTIONS, Nursing Mothers). Alternative antiasthma medication should be considered in such patients.

The bioavailability of ACCOLATE may be decreased when taken with food. Patients should be instructed to take ACCOLATE at least 1 hour before or 2 hours after meals.

Patients should be told that a rare side effect of ACCOLATE is elevation of liver enzymes and that if they experience signs and/or symptoms of liver dysfunction (e.g., right upper quadrant abdominal pain, nausea, fatigue, lethargy, pruritus, jaundice, and flu-like symptoms), they should contact their physician immediately.

Hepatic: Rarely, elevations of one or more liver enzymes may occur during ACCOLATE therapy. Most of these have been observed in clinical trials with ACCOLATE at doses four times higher than the recommended dose. The clinical significance of these elevations are unknown. Cases of symptomatic hepatitis and hyperbilirubinemia without other attributable cause, have occurred in patients who have received the recommended dose of ACCOLATE (40 mg/day). In rare cases, patients have progressed to hepatic failure. In most, but not all patients, the clinical symptoms abated and the liver enzymes returned to normal or near normal after stopping ACCOLATE. If clinical signs or symptoms of liver dysfunction (e.g., right upper quadrant abdominal pain, nausea, fatigue, lethargy, pruritus, jaundice, and flu-like symptoms) are noted, it is reasonable to recommend that standard liver tests be obtained and the patient managed accordingly. A decision to discontinue ACCOLATE should be individualized to the patient's condition weighing the risk of hepatic dysfunction against the clinical benefit of ACCOLATE to the patient. (See PRECAUTIONS, Information for Patients and ADVERSE REACTIONS sections.)

Eosinophilic Conditions: In rare cases, patients on ACCOLATE therapy may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic steroid therapy. These events usually, but not always, have been associated with the reduction of oral steroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between ACCOLATE and these underlying conditions has not been established. (See ADVERSE REACTIONS.)

Drug Interactions: In a drug interaction study in 16 healthy male volunteers, coadministration of multiple doses of zafirlukast (160 mg/day) to steady state with a single 25-mg dose of warfarin resulted in a significant increase in the mean AUC (+63%) and half-life (+36%) of S-warfarin. The mean prothrombin time (PT) increased by approximately 35%. This interaction is probably due to an inhibition by zafirlukast of the cytochrome P450 2C9 isoenzyme system. Patients on oral warfarin anticoagulant therapy and ACCOLATE should have their prothrombin times monitored closely and anticoagulant dose adjusted accordingly (see WARNINGS). No formal drug-drug interaction studies with ACCOLATE and other drugs known to be metabolized by the cytochrome P450 2C9 isoenzyme (e.g., tolbutamide, phenytoin, carbamazepine) have been conducted; however, care should be exercised when ACCOLATE is co-administered with these drugs.

(CONTINUED ON REVERSE SIDE)

In a drug interaction study in 16 healthy male volunteers, co-administration of zafirlukast (320 mg/day), with terfenadine (60 mg twice daily) to steady state resulted in a decrease in the mean C_{max} (-66%) and AUC (-54%) of ACCOLATE. No effect of zafirlukast on terfenadine plasma concentrations or ECG parameters (i.e., QTc interval) was seen. No formal drug-drug interaction studies between ACCOLATE and other drugs known to be metabolized by the P450 3A4 (CYP 3A4) isoenzyme (e.g., dihydropyridine calcium-channel blockers, cyclosporin, cisapride, astemizole) have been conducted. As ACCOLATE is known to be an inhibitor of CYP 3A4 in vitro, it is reasonable to employ appropriate clinical monitoring when these drugs are coadministered with ACCOLATE.

In a drug interaction study in 11 asthmatic patients, co-administration of a single dose of zafirlukast (40 mg) with erythromycin (500 mg three times daily for 5 days) to steady state resulted in decreased mean plasma levels of zafirlukast by approximately 40% due to a decrease in zafirlukast bioavailability.

Co-administration of zafirlukast (80 mg/day) at steady state with a single dose of a liquid theophylline preparation (6 mg/kg) in 13 asthmatic patients resulted in decreased mean plasma levels of zafirlukast by approximately 30%, but no effect on plasma theophylline levels was observed. Rare cases of patients experiencing increased theophylline levels with or without clinical signs or symptoms of theophylline toxicity after the addition of ACCOLATE to an existing theophylline regimen have been reported. The mechanism of the interaction between ACCOLATE and theophylline in these patients is unknown (see ADVERSE REACTIONS).

Co-administration of zafirlukast (40 mg/day) with aspirin (650 mg four times daily) resulted in mean increased plasma levels of zafirlukast by approximately 45%.

In a single-blind, parallel-group, 3-week study in 39 healthy female subjects taking oral contraceptives, 40 mg twice daily of zafirlukast had no significant effect on ethinyl estradiol plasma concentrations or contraceptive efficacy.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In two-year carcinogenicity studies, zafirlukast was administered at oral daily doses of 10, 100, and 300 mg/kg to mice and 40, 400, and 2000 mg/kg to rats. Male mice given 300 mg/kg/day of zafirlukast had a greater incidence of hepatocellular adenomas as compared to concurrent controls; female mice at this dose showed a greater incidence of whole body histocytic sarcomas. Male and female rats given 2000 mg/kg/day of zafirlukast had a greater incidence of urinary bladder transitional cell papillomas as compared to concurrent controls. Pharmacokinetic data show that the plasma concentrations in mice at non-tumorigenic (100 mg/kg) and tumorigenic (300 mg/kg) doses of zafirlukast were approximately 70 times and 220 times, respectively, the plasma concentrations at the maximum recommended human daily oral dose. For rats, plasma concentrations at the non-tumorigenic (400 mg/kg) and tumorigenic (2000 mg/kg) doses of zafirlukast were approximately 170 times and 200 times, respectively, the plasma concentrations in humans at the maximum recommended human daily oral dose. The clinical significance of these findings for the long-term use of ACCOLATE is unknown.

In mutagenicity studies, there was no evidence of mutagenic potential in reverse (*S. typhimurium* and *E. coli*) or forward point mutation (CHO-HGPRT and mouse lymphoma) assays or in two assays for chromosomal aberrations (human peripheral blood lymphocyte clastogenic assay and the rat bone marrow micronucleus assay).

Reproduction and fertility studies in rats showed no effect on fertility due to zafirlukast at doses up to 2000 mg/kg (approximately 400 times the maximum recommended human daily oral dose on mg/m² basis). In the one-year toxicity studies in dogs, zafirlukast produced an increase in absolute and relative uterine and ovarian weights at an oral dose of 150 mg/kg, resulting in approximately 85 times the systemic exposure (AUC_{0-12h}) in humans at the maximum recommended human oral daily dose.

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 daily oral dose on a mg/m² basis), 2000 mg/kg/day in rats (approximately 400 times the maximum recommended human daily oral dose on a mg/m² basis) and 2000 mg/kg/day in cynomolgus monkeys (approximately 800 times the maximum recommended human daily oral dose on a mg/m² basis). At 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 a maternally toxic dose of 2000 mg/kg/day orally. There are no adequate and well-controlled trials in pregnant women. Because animal reproduction studies are not always predictive of human response, ACCOLATE should be used during pregnancy only if clearly needed.

Nursing Mothers: Zafirlukast is excreted in breast milk. Following repeated 40-mg twice-a-day dosing in healthy women, average steady-state concentrations of zafirlukast in breast milk were 50 ng/mL compared to 255 ng/mL in plasma. Because of the potential for tumorigenicity shown for zafirlukast in mouse and rat studies and the enhanced sensitivity of neonatal rats and dogs to the adverse effects of zafirlukast, ACCOLATE should not be administered to mothers who are breast-feeding.

Pediatric Use: The safety and effectiveness of ACCOLATE in pediatric patients below the age of 12 years have not been established.

ADVERSE REACTIONS

The safety database for ACCOLATE consists of more than 4,000 healthy volunteers and patients who received ACCOLATE, of which 1723 were asthmatics enrolled in trials of 13 weeks duration or longer. A total of 671 patients received ACCOLATE for 1 year or longer. The majority of the patients were 18 years of age or older; however 222 patients between the age of 12 and 18 years received ACCOLATE.

A comparison of adverse events reported by ≥ 1% of zafirlukast-treated patients, and at rates numerically greater than in placebo-treated patients, is shown for all trials in the table below.

Table 2

Adverse Event	ACCOLATE N=4058	PLACEBO N=2032
Headache	12.9%	11.7%
Infection	3.5%	3.4%
Nausea	3.1%	2.0%
Diarrhea	2.8%	2.1%
Pain (generalized)	1.9%	1.7%
Asthenia	1.8%	1.6%
Abdominal Pain	1.8%	1.1%
Accidental Injury	1.6%	1.5%
Dizziness	1.6%	1.5%
Myalgia	1.6%	1.5%
Fever	1.6%	1.1%
Back Pain	1.5%	1.2%
Vomiting	1.5%	1.1%
SGPT Elevation	1.5%	1.1%
Dyspepsia	1.3%	1.2%

The frequency of less common adverse events was comparable between ACCOLATE and placebo.

Rarely, elevations of one or more liver enzymes have occurred in patients receiving ACCOLATE in controlled clinical trials. Most of these have been observed in asymptomatic patients at doses four times higher than the recommended dose and returned to the normal range after a variable period of time upon discontinuation of ACCOLATE therapy. Cases of symptomatic hepatitis and hyperbilirubinemia, without other attributable cause, have occurred in patients who have received the recommended daily dose of ACCOLATE (40mg/day). In rare cases, patients have progressed to hepatic failure. In most, but not all patients, the clinical symptoms abated and the liver enzymes returned to normal or near normal after stopping ACCOLATE.

In clinical trials, an increased proportion of zafirlukast patients over the age of 55 years reported infections as compared to placebo-treated patients. A similar finding was not observed in other age groups studied. These infections were mostly mild or moderate in intensity and predominantly affected the respiratory tract. Infections occurred equally in both sexes, were dose-proportional to total milligrams of zafirlukast exposure, and were associated with coadministration of inhaled corticosteroids. The clinical significance of this finding is unknown.

In rare cases, patients on ACCOLATE therapy may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic steroid therapy. These events usually, but not always, have been associated with the reduction of oral steroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between ACCOLATE and these underlying conditions has not been established. (See PRECAUTIONS - Eosinophilic Conditions.)

Hypersensitivity reactions, including urticaria, angioedema and rashes, with or without blistering, have been reported in association with ACCOLATE therapy. Additionally, there have been reports of patients experiencing agranulocytosis, bleeding, bruising, or edema in association with ACCOLATE therapy.

Rare cases of patients experiencing increased theophylline levels with or without clinical signs or symptoms of theophylline toxicity after the addition of ACCOLATE to an existing theophylline regimen have been reported. The mechanism of the interaction between ACCOLATE and theophylline in these patients is unknown and not predicted by available *in vitro* metabolism data and the results of a clinical drug interaction study. (See CLINICAL PHARMACOLOGY and PRECAUTIONS - Drug Interactions sections.)

OVERDOSAGE

No deaths occurred at oral zafirlukast doses of 2000 mg/kg in mice (approximately 200 times the maximum recommended human daily oral dose on a mg/m^2 basis), 2000 mg/kg in rats (approximately 400 times the maximum recommended human daily oral dose on a mg/m^2 basis), and 500 mg/kg in dogs (approximately 330 times the maximum recommended human daily oral dose on a mg/m^2 basis).

There is no experience to date with zafirlukast overdose in humans. It is reasonable to employ the usual supportive measures in the event of an overdose; e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required.

DOSAGE AND ADMINISTRATION

The recommended dose of ACCOLATE is 20 mg twice daily in adults and children 12 years and older. Since food reduces the bioavailability of zafirlukast, ACCOLATE should be taken at least 1 hour before or 2 hours after meals.

Elderly Patients: Based on cross-study comparisons, the clearance of zafirlukast is reduced in elderly patients (65 years of age and older), such that C_{max} and AUC are approximately twice those of younger adults. In clinical trials, a dose of 20 mg twice daily was not associated with an increase in the overall incidence of adverse events or withdrawals because of adverse events in elderly patients.

Patients with Hepatic Impairment: The clearance of zafirlukast is reduced in patients with stable alcoholic cirrhosis such that the C_{max} and AUC are approximately 50 - 60% greater than those of normal adults. ACCOLATE has not been evaluated in patients with hepatitis or in long-term studies of patients with cirrhosis.

Patients with Renal Impairment: Dosage adjustment is not required for patients with renal impairment.

Pediatric Patients: The safety and effectiveness of ACCOLATE in pediatric patients below the age of 12 years have not been established.

HOW SUPPLIED

20 mg Tablets, (NDC 0310-0402) white, round, biconvex, coated tablets identified with "ZENECA" debossed on one side and "ACCOLATE 20" debossed on the other side are supplied in opaque HDPE bottles of 60 tablets and hospital Unit Dose blister packages of 100 tablets.

Store at controlled room temperature, (20°-25°C) (68°-77°F) [see USP]. Protect from light and moisture. Dispense in the original air-tight container.

ZENECA

Manufactured for:
Zeneca Pharmaceuticals
A Business Unit of Zeneca Inc.
Wilmington, Delaware 19850-5437
By: IPR Pharmaceuticals Inc.
Carolina, Puerto Rico 00984-1967

670006 Rev H 03/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20547/S008

MEDICAL REVIEW(S)

DEC 11 8 1998

MEDICAL OFFICER REVIEW

DIVISION OF PULMONARY DRUG PRODUCTS (HFD-570)

APPLICATION #: ~~20-547/SLR-008~~ APPLICATION TYPE: Labeling Supplement

SPONSOR: ~~Merck~~ Zeneca PROPRIETARY NAME: Accolate

CATEGORY OF DRUG: ~~LTD4~~ antagonist USAN / Established Name: zafirlukast

ROUTE: oral

MEDICAL REVIEWER: Honig REVIEW DATE: December 8, 1998

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
September 21, 1998	September 22, 1998	Labeling supplement	
November 3, 1998	November 5, 1998	Response to FDA request for information	
November 2, 1998	November 3, 1998	Periodic Safety Update Report	

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:

Overview of Application/Review: This review concerns proposed revisions to the zafirlukast product label. This submission is in follow-up to a safety meeting with the sponsor on June 22, 1998 at which time it was agreed that four safety issues were to be addressed in revised product labeling. These include bleeding/bruising, agranulocytosis, liver effects, and edema.

This review has two purposes. First, it will summarize the submission of November 3, 1998 which contains a comprehensive review of the liver function data/events that have been collected for zafirlukast. The second objective of the review is to assess the adequacy of the proposed labeling language.

Outstanding Issues: Zafirlukast/bleeding time study

Recommended Regulatory Action: FAX to sponsor

New Clinical Studies: _____ Clinical Hold _____ Study May Proceed

NDAs:

Efficacy / Label Supp.: ___x___ Approvable _____ Not Approvable

Signed: Medical Reviewer: Date: 12/8/98

Medical Team Leader Date: 12/15/98

1fx

Background:

A meeting to discuss the occurrence of systemic eosinophilia in association with Accolate use was held on June 22, 1998. At that meeting, reports of bruising/bleeding, liver toxicity, and edema were also discussed. In follow-up to that meeting, Zeneca was asked to prepare a comprehensive review of the effects of Accolate on the liver as well as to submit proposed draft labeling to address the aforementioned safety concerns. This is the major focus of this review.

Accolate and the Liver:

In response to the FDA request, Zeneca prepared a review of the clinical trials experience as well as a summary of the post-approval reports of hepatic events in association with Accolate use.

Clinical Trials:

Much of the clinical trial data have been addressed in the MOR safety review of the original NDA submission. The information submitted contains data from the on-going clinical trials program through June 30, 1998. Subjects with pre-existing liver disease were generally excluded from participation in clinical trials; however, some data exists from patients who entered clinical trials with preexisting liver disease (protocol violators) or from a clinical pharmacology trial specifically designed to address the influence of hepatic disease on zafirlukast pharmacokinetics. The LFT response in this small subset was similar to that seen in the larger clinical trials database described below.

Up to June 30, 1998, a large number of subjects had received zafirlukast in clinical trials (9283). Placebo-treated patients number 3711. The plurality of zafirlukast patients received the approved dose (40 mg/day) although a large number of patients received 160 mg/day for long periods of time (767 patients for 100 days and 398 patients for up to one year). The LFT experience from these trials are summarized in the table below.

		All Clinical Trials (double-blind and open-label periods)					
		2 to ≤3xULN		>3 to ≤5xULN		>5x ULN	
	Overall N	N	% of subjects	N	% of subjects	N	% of subjects
Placebo	3711	30	0.8	13	0.4	7	0.2
<40 mg/day	1507	6	0.4	8	0.5	1	0.1
40 mg/day	4045	52	1.3	28	0.7	10	0.2
80 mg/day	1462	15	1.0	6	0.4	0	0.0
160 mg/day	2025	37	1.8	25	1.2	32	1.6
Other	244	1	0.4	1	0.4	0	0.0
Total	9283	111	1.2	68	0.7	43	0.5

Reviewer comment: The above table does not take into account the different amount of time the patients have been exposed to zafirlukast and placebo. The chance of having a spontaneous LFT elevation is directly proportional to the amount of time observed and the number of samples obtained over time. Therefore, an alternative analysis would incorporate life-table analyses as shown in Appendices A, B, and C. In these analyses, it is apparent that the probability of having a defined LFT elevation is greater than placebo at zafirlukast doses of 160 mg/day. For lower doses, the probability of having a defined elevation is comparable to placebo. Of the 50 patients with ALT> 5xULN, 29 (58%) were female. Of the 43 zafirlukast-treated patients, 27 (63%) were female. Of the seven placebo-treated patients, only 2 (29%) were female. There were not age-related differences in LFT elevations. Similarly, there did not appear to be any correlation between the risk of defined LFT elevation and pre-treatment LFT values.

Of those patients with LFT elevation in the clinical trials database, 11 patients had changes consistent with toxic or drug-induced hepatitis. The criteria for making this determination included the lack of other contributing factors, the rate and degree of elevation, positive dechallenge, and the pattern of AST/ALT elevation. Nine of these patients received 160 mg/day of zafirlukast. The other two patients received 40 or 80 mg/day. All but one patient was female.

Reviewer conclusions from clinical trials experience:

The risk of defined LFT elevations and/or zafirlukast-induced hepatitis appears to be greater at doses of 160 mg/day and this risk appears to be greater in females.

Post-Marketing Experience:

As of June 30, 1998, Accolate was approved for marketing in 20 countries. In the United States, it is estimated that over one million patients have received Accolate with a mean exposure of 140 days. Approximately 520,000 patients have received Accolate for more than 9 months. Through June 30, a total of 90 spontaneous reports of liver-related AEs have been received. These fall into the following categories:

-42 reports of elevated LFTs (non-serious)
-38 reports of potential hepatitis (including one death)
-3 reports of liver failure (including one death)
-7 miscellaneous reports (including one fatty liver, one hepatosplenomegaly, and 5 non-specified)

For the purposes of interpretation, hepatitis was defined as having symptom or signs of clinical hepatitis or documented ALT > 5xULN. These reports are well summarized in tabular and narrative format in the Zeneca document. The cases of hepatitis cover a wide variety of clinical patterns without consistency of signs, symptoms or temporal relationships. Most patients were symptomatic and jaundiced. Many had significant confounding factors and causality is difficult to assess. As mentioned, there were 3 reports of liver failure after exposure to zafirlukast, one of which resulted in a fatality. This involved a 67 year old woman who received Accolate concomitantly with allopurinol for gout. She developed an exfoliative rash after one month of zafirlukast followed by hepatic failure and hepatorenal syndrome. Since these are both consistent with allopurinal toxicity, a causal relationship to Accolate is difficult to establish.

The second report involved a 45 year old female who took Accolate for 3 months and experienced acute liver failure and hepatic necrosis. Her lab values peaked at AST= 1617 and ALT= 1473 with a bilirubin of 8.7 and a prothrombin time of 15.7 seconds. Accolate was discontinued and she eventually improved over a period of three months. A liver biopsy was performed one month after presenting and revealed extensive necrosis that was thought to be drug-induced. ANA was positive at 1:320. The patient has a long history of hypothyroidism, asthma and eczema and takes synthroid, salmeterol, flunisolide, cromolyn and theophylline. The third report remains largely unsubstantiated with follow-up not obtainable.

Reviewer comment: Since June 30, 1998, at least two additional reports involving hepatic failure in association with Accolate use have been received. These are summarized below.

Manufacturer's # 1998UW48388: This report involves a 49 year old female who presented to her LMD with complaints of fatigue. Increased LFTs were noted. One week later the patient progressed to jaundice. The bilirubin was as high as 39 two weeks after presenting with her complaints. On admission to the hospital she was noted to have a disseminated macular rash which was thought to be toxic epidermal necrolysis. The patient carried a diagnosis of hepatic failure and was being evaluated for a liver transplant. A biopsy revealed a mixed eosinophilic and lymphocytic infiltrate. Connective tissue workup and ceruloplasmin levels were normal. Her only other medical problem is asthma for which she received theophylline, Flovent and Atrovent. Eventually, the patient underwent transplantation. Pathology on the native liver confirmed the previous findings, which was felt to be consistent with autoimmune hepatitis. The pathologist felt that this was inconsistent with drug induced hepatitis because the patient had been off drug for too long a period (6 weeks) to explain the degree of inflammation.

Manufacturer's # 1998UW47794: This reports involves a 44 year old female who was hospitalized after developed clinical symptoms and jaundice. She was otherwise healthy and denies alcohol use. The clinical picture worsened despite discontinuation of Accolate. The transaminases were in the 1000 level and the bilirubin was >20. A biopsy revealed submassive necrosis of the liver characterized as a 'classic drug reaction.' The patient was empirically treated with high dose corticosteroids and the patient eventually recovered.

Reviewer comment: These are compelling cases of hepatic failure and dysfunction in otherwise healthy females without confounding drugs. The temporal relationships are consistent with drug induced disease. Hepatic failure associated with Accolate use should be represented in the product label.

Other safety issues to be addressed in the labeling supplement:

Edema: To date, there are a total of 51 cases of zafirlukast-associated edema. Most of these are non-serious. Since one case had a positive rechallenge, Zeneca agrees to include it in the ADVERSE REACTIONS section of the label.

Agranulocytosis: There have been several reports to the safety postmarketing database. The sponsor has agreed to include it in the ADVERSE REACTIONS section.

Bleeding/bruising events: These were discussed extensively at the FDA/Zeneca meeting in June 1998. Although it was clear that there was a lack of consistency of a clinical pattern to these cases, many had positive dechallenge and some had a positive rechallenge. Several cases involved increased ease of bruising and one case had a documented abnormal bleeding time which normalized upon dechallenge. Although coagulation parameters were not affected in patients studied in controlled trials, no study of the effect of zafirlukast on bleeding time has been performed. The sponsor agreed to perform this study.

Reviewer comment: All of the above deserve mention in the product label. The sponsor should be reminded of their commitment to perform the clinical pharmacology/bleeding time study.

PROPOSED REVISED PRODUCT LABELING:

The sponsor has only proposed changing the ADVERSE REACTION section of the product label as follows.

Current:

4th paragraph:

Rarely, elevations of one or more liver enzymes have occurred in patients receiving Accolate in controlled clinical trials. Most of these have been observed in asymptomatic patients at doses four times higher than the recommended dose and returned to the normal range after a variable period of time upon discontinuation of Accolate therapy. Rare cases of symptomatic hepatitis and hyperbilirubinemia, without other attributable cause, have occurred in patients who had received the recommended doses of Accolate (40 mg/day). In these patients, the liver enzymes returned to normal or near normal after stopping Accolate.

8th paragraph:

Rare cases of patients.....and the results of a drug interaction study (see CLINICAL PHARMACOLOGY and PRECAUTIONS, Drug Interactions).

Proposed:

4th paragraph:

8th paragraph:

Reviewer comments: The proposed labeling revisions are unacceptable. In fact, the revisions to the paragraph describing the LFT elevations and hepatitis are less informative than the existing language. The description of bruising, bleeding, agranulocytosis and edema should also be revised and be incorporated as the last sentence of the 7th paragraph. FDA proposed revisions are highlighted below.

4th paragraph:

Rarely, elevations of one or more liver enzymes have occurred in patients receiving Accolate in controlled clinical trials. Most of these have been observed in asymptomatic patients at doses four times higher than the recommended dose and returned to the normal range after a variable period of time upon discontinuation of Accolate therapy. ~~Rare c~~Cases of symptomatic hepatitis and hyperbilirubinemia *with some patients progressing to hepatic failure*, without other attributable cause, have occurred in patients who had received the recommended doses of Accolate (40 mg/day). In most, *but not all patients, the clinical symptoms abated and* the liver enzymes returned to normal or near normal after stopping Accolate.

7th paragraph:
Hypersensitivity reactions, including urticaria, angioedema and rashes, with and without blistering, have been reported in association with Accolate therapy. *Additionally, cases of patients experiencing agranulocystosis, bleeding, bruising or edema in association with Accolate therapy have been reported.*

Rare cases of patients.....and the results of a drug interaction study (see CLINICAL PHARMACOLOGY and PRECAUTIONS, Drug Interactions).

REVIEWER RECOMMENDATION:

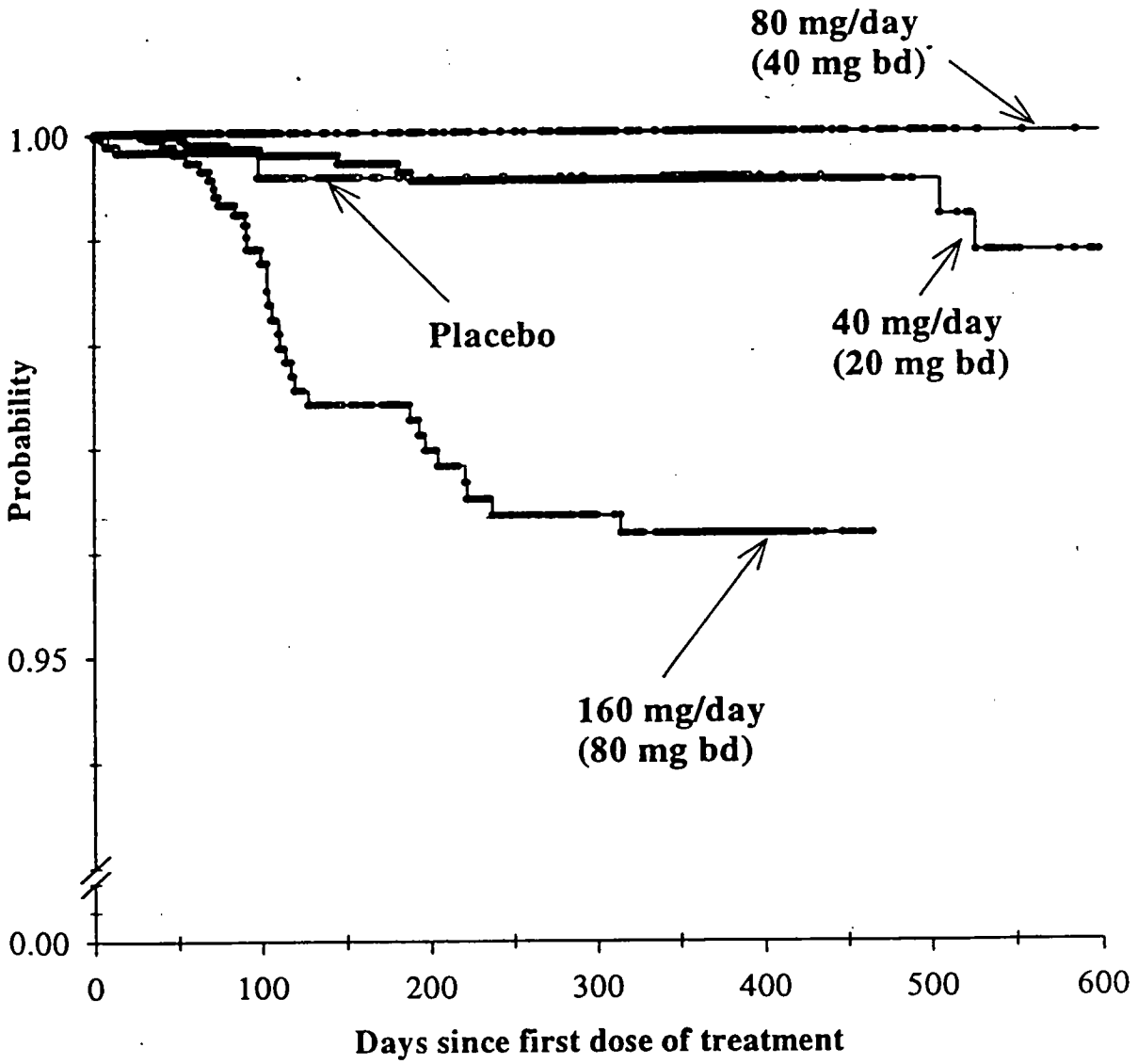
1. The aforementioned labeling revisions should be forwarded and the sponsor.
2. The sponsor should be reminded of their obligation to perform a study investigating the effect of Accolate therapy on bleeding time.

cc:

HFD-570/NDA 20-547/Division File
HFD-570/MO/Honig/Anthracite/Trontell
HFD-570/PM/Jani

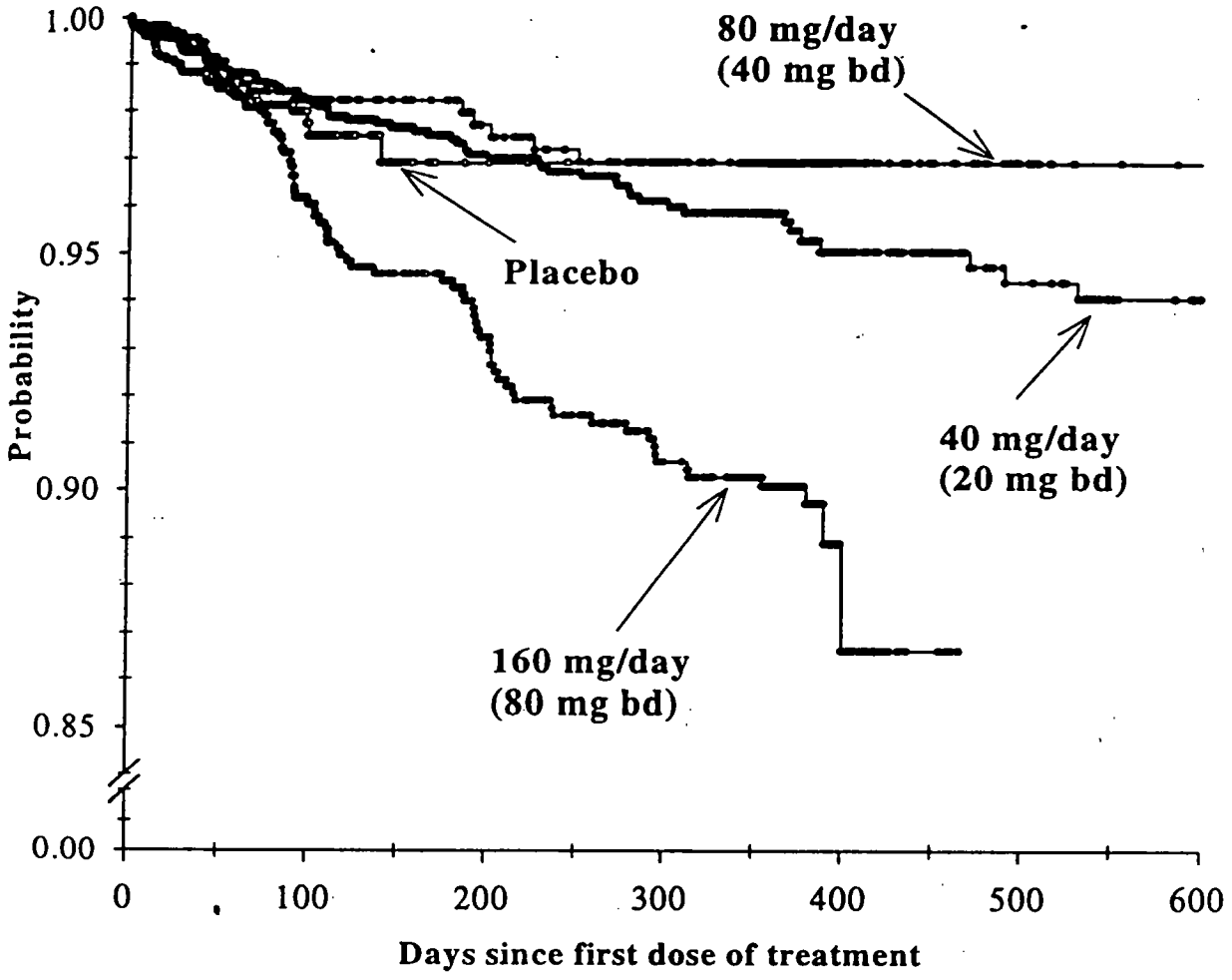
Appendix A

Figure 1 **Kaplan-Meier cumulative occurrence function: comparison of doses with respect to time to first ALT elevation >5xULN**



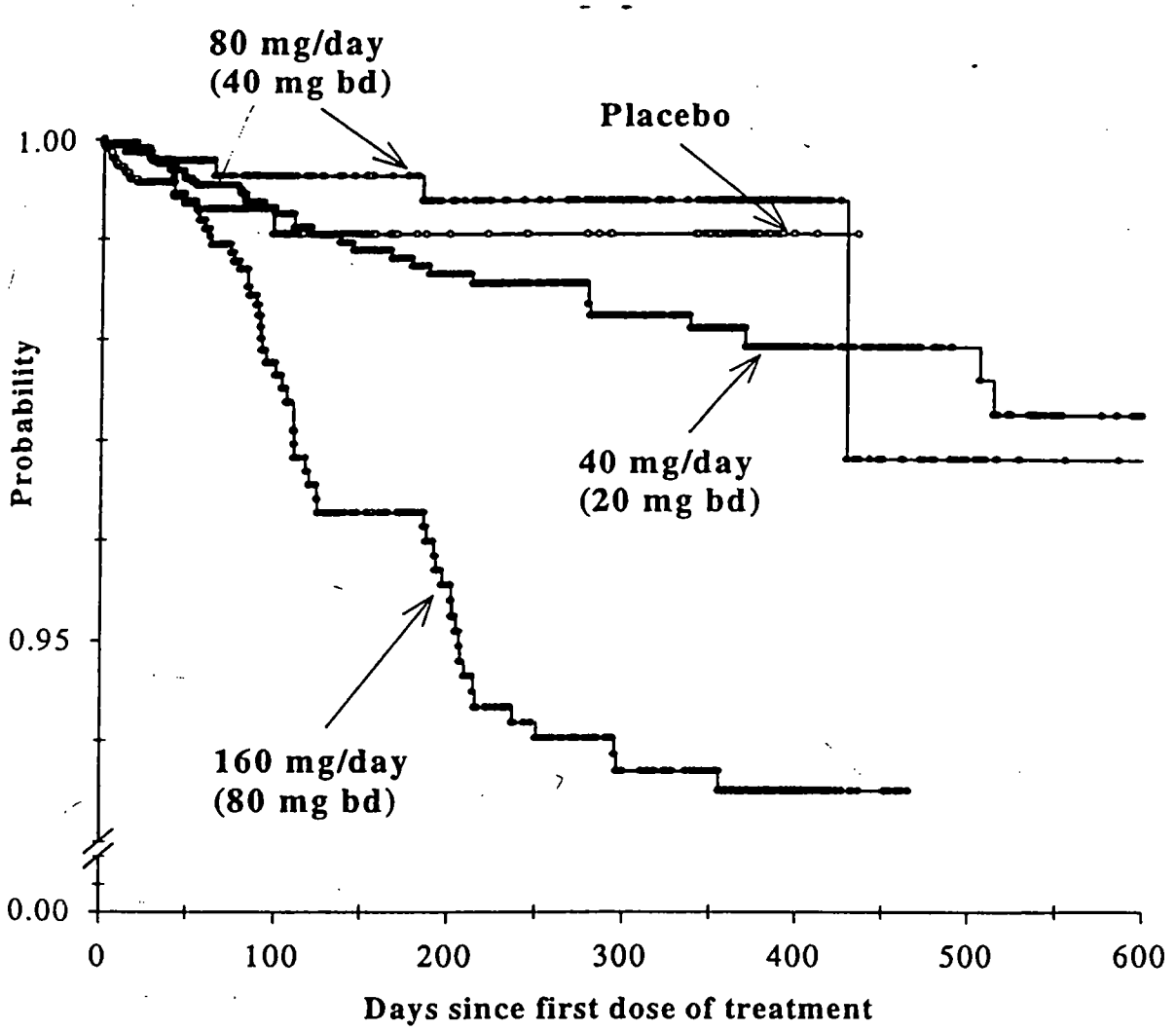
Appendix B

Figure 2 **Kaplan-Meier cumulative occurrence function: comparison of doses with respect to time to first ALT elevation >2xULN**



Appendix C

Figure 3 Kaplan-Meier cumulative occurrence function: comparison of doses with respect to time to first ALT elevation >3xULN



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20547/S008

ADMINISTRATIVE DOCUMENTS

APR 2 3 1999

Project Manager's Labeling Review

NDA 20-547/ S-008 FA

Product: Accolate Tablets

Sponsor: Zeneca Pharmaceuticals

Date submitted: April 7, 1999

The Final Printed Labeling (FPL) submitted on April 7, 1999, is identical to the labeling approved on March 17, 1999. The labeling should be acknowledged and retained.

Parinda Jani
Project Manager

CC:
ORIG NDA 20-547
DIV FILE/HFD-570
HFD-570/JANI

4/23/99.

MAR 1 6 1999

PROJECT MANAGER'S LABELING REVIEW

NDA: 20-547/S-008
Project Manager: Parinda Jani
PRODUCT: ACCOLATE (zafirlukast) Tablets 20 mg
SPONSOR: Zeneca Pharmaceuticals
SUBMISSION DATE: September 21, 1998
January 20, 1999
March 12, 1999

On September 21, 1998, Zeneca submitted supplement S-008, which provides for a revised package insert with changes to the ADVERSE REACTIONS section and the Hepatic subsection of the PRECAUTIONS section. The supplement was amended January 20 and March 12, 1999 to incorporate the changes recommended by the Division.

PRECAUTIONS: Hepatic:
Current: Rarely, elevations of one or more liver enzymes may occur during ACCOLATE therapy. Most of these have been observed in clinical trials with ACCOLATE at doses four times higher than the recommended dose. The clinical significance of these elevations are unknown. If clinical signs or symptoms .....(See PRECAUTIONS: Information for Patients and ADVERSE REACTIONS sections.)

Revised to: Rarely, elevations of one or more liver enzymes may occur during ACCOLATE therapy. Most of these have been observed in clinical trials with ACCOLATE at doses four times higher than the recommended dose. The clinical significance of these elevations are unknown. Cases of symptomatic hepatitis and hyperbilirubinemia without other attributable cause, have occurred in patients who have received the recommended dose of ACCOLATE (40 mg/day). In rare cases, patients have progressed to hepatic failure. In most, but not all patients, the clinical symptoms abated and the liver enzymes returned to normal or near normal after stopping ACCOLATE. If clinical signs or symptoms .....(See PRECAUTIONS: Information for Patients and ADVERSE REACTIONS sections.)

ADVERSE REACTIONS
4th paragraph: Current: Rarely, elevations of one or more liver enzymes have occurred in patients receiving ACCOLATE in controlled clinical trials. Most of these have been observed in asymptomatic patients at doses four times higher than the recommended dose and returned to the normal range after a variable period of time upon discontinuation of ACCOLATE therapy. Rare cases of symptomatic hepatitis and hyperbilirubinemia, without other attributable cause, have occurred in patients who have received the recommended dose of ACCOLATE (40 mg/day). In these patients, the liver enzymes returned to normal or near normal after stopping ACCOLATE.

Revised to: Rarely, elevations of one or more liver enzymes have occurred in patients receiving ACCOLATE in controlled clinical trials. Most of these have been observed in asymptomatic

patients at doses four times higher than the recommended dose and returned to the normal range after a variable period of time upon discontinuation of ACCOLATE therapy. Cases of symptomatic hepatitis and hyperbilirubinemia, without other attributable cause, have occurred in patients who have received the recommended daily dose of ACCOLATE (40 mg/day). In rare cases, patients have progressed to hepatic failure. In most, but not all patients, the clinical symptoms abated and the liver enzymes returned to normal or near normal after stopping ACCOLATE.

7th paragraph: Current: Hypersensitivity reactions, including urticaria, angioedema, and rashes, with or without blistering, have been reported in association with ACCOLATE therapy.

Revised to: Hypersensitivity reactions, including urticaria, angioedema, and rashes, with or without blistering, have been reported in association with ACCOLATE therapy. Additionally, there have been reports of patients experiencing agranulocytosis, bleeding, bruising or edema in association with ACCOLATE therapy.

There were no changes made to the remainder sections.

Recommendation: Supplement S-008 should be approved, as amended, March 12, 1999. Draft approval letter is attached.

Parinda Jani
Project Manager

3-16-99
Date

Raymond Anthracite, M.D.
Medical Officer

CONCUR

3/16/99
Date

CC:
ORIG NDA 20-547
DIV FILE/HFD-570
HFD-570/JANI/3-16-99
HFD-570/SCHUMAKER
HFD-570/ANTHRACITE
HFD-570/JENKINS

3/16/99.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20547/S008

CORRESPONDENCE

DiV file

APR 2 8 1999

NDA 20-547/S-008

Zeneca Pharmaceuticals
1800 Concord Pike
P.O.Box 15437
Wilmington, Delaware 19850-5437

Attention: Kevin McKenna, Ph.D.
Manager, Marketed Products
Drug Regulatory Affairs Department

Dear Dr. McKenna:

We acknowledge the receipt of your April 7, 1999, submission containing final printed labeling in response to our March 17, 1999, letter approving your supplemental new drug application for Accolate (zafirlukast) Tablets, 20 mg.

We have reviewed the labeling that you have submitted in accordance with our March 17, 1999, letter, and we find it acceptable.

If you have any questions, contact Ms. Parinda Jani, Project Manager, at (301) 827-1064.

Sincerely yours,

John K. Jenkins, M.D., F.C.C.P.
Acting Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CC:
ORIGINAL NDA 20-547
HFD-570/DIV FILES
HFD-570/P.JANI
HFD-570/SCHUMAKER/4-23-99
HFD-570/ANTHRACITE/
HFD-102 (WITH LABELING)
DISTRICT OFFICE
HF-2/MEDWATCH (WITH LABELING)
HFD-92 (WITH LABELING)
HFD-40/S.SHERMAN (WITH LABELING)
HFD-613 (WITH LABELING)
HFD-735 (WITH LABELING)
HFD-820/Y.Y.CHIU
HFD-21/J.TREACY

ACKNOWLEDGE AND RETAIN (AR)

4/26/99