CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-547/S011

APPROVAL LETTER

NDA 20-547/S-011

FEB 7 2000

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 August 10, 1999, received August 11, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Accolate (zafirlukast) 10 mg and 20 mg Tablets.

We acknowledge receipt of your submission dated November 29, 1999.

This supplemental new drug application provides for a revised Geriatric Use subsection of the PRECAUTIONS section.

We have completed the review of this supplemental application and it is approved effective on the date of this letter. As agreed to by you, the Geriatric Use subsection of the PRECAUTIONS section will be revised as follows:

> Based on cross study comparison, the clearance of zafirlukast is reduced in patients 65 year of age and older such that Cmax and AUC are approximately 2- to 3-fold greater than those of younger patients (see DOSAGE AND ADMINISTRATION, and CLINICAL PHARMACOLOGY sections).
>
> A total of 8094 patients were exposed to zafirlukast in North American and European short-term placebo-controlled clinical trials. Of these, 243 patients were elderly (age 65 years and older). No overall difference in adverse events was seen in the elderly patients, except for an increase in the frequency of infection among zafirlukast treated elderly patients compared to placebo treated elderly patients (7.0% vs 2.9%). The infections were not severe, occurred mostly in the lower respiratory tract, and did not necessitate withdrawal of therapy.

An open-label, uncontrolled, 4-week trial of 3759 asthma patients compared the safety and efficacy of ACCOLATE 20 mg given twice daily in three patient age groups; adolescents (12-17 years), adults (18-65 years), and elderly (greater than 65 years). A higher percentage of elderly patients (n=384) reported adverse events when compared to adults and adolescents. These elderly patients showed less improvement in the efficacy measures. In the elderly patients, adverse events occurring in greater than 1% of the population included headache (4.7%), diarrhea and nausea (1.8%), and pharyngitis (1.3%). The elderly reported the lowest percentage of infections of all three age groups in this study.

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted draft labeling (package insert submitted November 29, 1999). These revisions are terms of the approval of this application.

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-011." 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, call Ms. Parinda Jani, Project Manager, at (301) 827-1064.

Sincerely yours,

/S/

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-547/S011

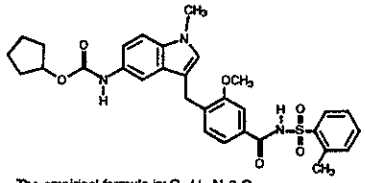
FINAL PRINTED LABELING

PROFESSIONAL INFORMATION BROCHURE

ACCOLATE®
ZAFIRLUKAST

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-tolysulfonylbenzamide. 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 10 and 20 mg tablets for oral administration.

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

CLINICAL PHARMACOLOGY

Mechanism of Action: 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:

Absorption

Zafirlukast is rapidly absorbed following oral administration. Peak plasma concentrations are generally achieved 3 hours after oral administration. The absolute bioavailability of zafirlukast is unknown. In two separate studies, one using a high fat and the other a high protein meal, administration of zafirlukast with food reduced the mean bioavailability by approximately 40%.

Distribution

Zafirlukast is more than 99% bound to plasma proteins, predominantly albumin. The degree of binding was independent of concentration in the clinically relevant range. The apparent steady-state volume of distribution (V_{ss}/F) is approximately 70 L, suggesting moderate distribution into tissues. Studies in rats using radiolabeled zafirlukast indicate minimal distribution across the blood-brain barrier.

Metabolism

Zafirlukast is extensively metabolized. The most common metabolic products are hydroxylated metabolites which are excreted in the feces. The metabolites of zafirlukast identified in plasma are at least 90 times less potent as LTD_4 receptor antagonists than zafirlukast in a standard *in vitro* test of activity. *In vitro* studies using human liver microsomes showed that the hydroxylated metabolites of zafirlukast excreted in the feces are formed through the cytochrome P450 2C9 (CYP2C9) 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 total plasma concentrations. (see Drug Interactions)

Excretion

The apparent oral clearance (CL/f) of zafirlukast is approximately 20 L/h. Studies in the rat and dog suggest that biliary excretion is the primary route of excretion. Following oral administration of radiolabeled zafirlukast to volunteers, urinary excretion accounts for approximately 10% of the dose and the remainder is excreted in feces. Zafirlukast is not detected in urine.

In the pivotal bioequivalence study, the mean terminal half-life of zafirlukast is approximately 10 hours in both normal adult subjects and patients with asthma. In other studies, the mean plasma half-life of zafirlukast ranged from approximately 8 to 16 hours in both normal subjects and patients with asthma. The pharmacokinetics of zafirlukast are approximately linear over the range from 5 mg to 80 mg. Steady-state plasma concentrations of zafirlukast are proportional to the dose and predictable from single-dose pharmacokinetic data. Accumulation of zafirlukast in the plasma following twice daily dosing is approximately 45%.

The pharmacokinetic parameters of zafirlukast 20 mg administered as a single dose to 38 male volunteers are shown with the table below.

Mean (% Coefficient of Variation) pharmacokinetic parameters of zafirlukast following single 20 mg oral dose administration to male volunteers (n=36)

C_{max} ng/ml	t_{max}[1] h	AUC ng.h/mL	t1/2 h	CL/f L/h
326 (31.0)	2 (0.5-5.0)	1197 (34)	10.9 (75.6)	19.4 (32)

[1] Median and range

Special Populations

Gender: The pharmacokinetics of zafirlukast are similar in males and females. Weight-adjusted apparent oral clearance does not differ due to gender.

Race: No differences in the pharmacokinetics of zafirlukast due to race have been observed.

Elderly: The apparent oral clearance of zafirlukast decreases with 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.

Children: Following administration of a 20 mg dose of zafirlukast to 20 boys and girls between 7 and 11 years of age, a mean (% coefficient of variation) peak drug concentration of 601 ng/mL (45%) was obtained at about 2.5 hours. Zafirlukast systemic exposure as determined by mean AUC was 2027 ng.h/mL (38%). Weight unadjusted apparent clearance was 11.4 L/h (42%) which resulted in greater systemic drug exposure than that obtained in adults for an identical dose. Zafirlukast disposition was unchanged after multiple dosing (20 mg twice daily) in children and the degree of accumulation in plasma was similar to that observed in adults.

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

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

Drug Interactions: The following drug interaction studies have been conducted with zafirlukast. (see PRECAUTIONS: Drug Interactions)

- Co-administration of multiple doses of zafirlukast (160 mg/day) to steady state with a single 25 mg dose of warfarin (a substance of CYP2C9) resulted in a significant increase in the mean AUC (+63%) and half-life (+36%) of S-warfarin. The mean prothrombin time increased by approximately 35%. The pharmacokinetics of zafirlukast were unaffected by coadministration with warfarin.
- Co-administration of zafirlukast (80 mg/day) at steady state with a single dose of a liquid theophylline preparation (5 mg/kg) in 13 asthmatic patients, 18 to 44 years of age, resulted in decreased mean plasma concentrations of zafirlukast by approximately 30%, but no effect on plasma theophylline concentrations was observed.
- Co-administration of zafirlukast (20 mg/day) or placebo at steady state with a single dose of sustained release theophylline preparation (15 mg/kg) in 16 healthy boys and girls (6 through 11 years of age) resulted in no significant differences in the pharmacokinetic parameters of theophylline.
- Co-administration of zafirlukast dosed at 40 mg twice daily in a single-blind, parallel-group, 3-week study in 39 healthy female subjects taking oral contraceptives, resulted in no significant effect on ethinyl estradiol plasma concentrations or contraceptive efficacy.
- Co-administration of zafirlukast (40 mg/day) with aspirin (650 mg four times daily) resulted in mean increased plasma concentrations of zafirlukast by approximately 45%.
- Co-administration of a single dose of zafirlukast (40 mg) with erythromycin (500 mg three times daily for 5 days) to steady state in 11 asthmatic patients, resulted in decreased mean plasma concentrations of zafirlukast by approximately 40% due to a decrease in zafirlukast bioavailability.

Clinical Studies:

Three U.S. double-blind, randomized, placebo-controlled, 13-week clinical trials in 1,380 adults and children 12 years of age and older 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.

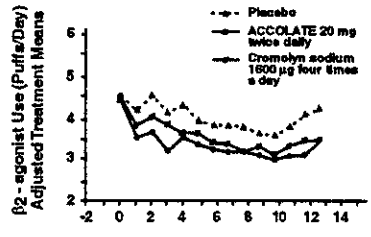
Table 1
Mean Change from Baseline at Study Endpoint

	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).

Mean β_2 - agonist use (puffs/day)



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 7 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.

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 hepatic dysfunction, and to contact their physician immediately if they experience symptoms of hepatic dysfunction (e.g., right upper quadrant abdominal pain, nausea, fatigue, lethargy, pruritus, jaundice, flu-like symptoms, and anorexia).

Hepatic: Rarely, elevations of one or more liver enzymes have occurred in patients receiving ACCOLATE in controlled clinical trials. In clinical trials, most of these have been observed at doses four times higher than the recommended dose. The following hepatic events (which have occurred predominantly in females) have been reported from postmarketing adverse event surveillance of patients who have received the recommended dose of ACCOLATE (40 mg/day): cases of symptomatic hepatitis (with or without hyperbilirubinemia) without other attributable cause, and rarely, hyperbilirubinemia without other elevated liver-function tests. In most, but not all, postmarketing reports, the patient's symptoms abated and the liver enzymes returned to normal or near normal after stopping ACCOLATE. In rare cases, patients have progressed to hepatic failure.

If liver dysfunction is suspected based upon clinical signs or symptoms (e.g., right upper quadrant abdominal pain, nausea, fatigue, lethargy, pruritus, jaundice, flu-like symptoms, anorexia, and enlarged liver) ACCOLATE should be discontinued. Liver function tests, in particular serum ALT, should be measured immediately and the patient managed accordingly. If liver function tests are consistent with hepatic dysfunction, ACCOLATE therapy should not be resumed. Patients in whom ACCOLATE was withdrawn because of hepatic dysfunction where no other attributable cause is identified should not be re-exposed to ACCOLATE. (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.

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 (20 mg/day) or placebo at steady state with a single dose of sustained release theophylline preparation (16 mg/kg) in 16 healthy boys and girls (6 through 11 years of age) resulted in no significant differences in the pharmacokinetic parameters of theophylline.

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, 18 to 44 years of age, 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

No formal drug-drug interaction studies between ACCOLATE and marketed drugs known to be metabolized by the P450 3A4 (CYP 3A4) isoenzyme (e g. dihydropyridine calcium-channel blockers, cyclosporin, cisapride) 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

Carcinogenesis, Mutagenesis, Impairment of Fertility: In two-year carcinogenicity studies, zafirlukast was administered at dietary 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 (approximately 75 times the maximum recommended daily oral dose in adults and in children based on a comparison of the plasma area-under the curves [AUCs] values of total drug exposure) showed an increased incidence of hepatocellular adenomas, female mice at this dose showed a greater incidence of whole body histocytic sarcomas Male and female rats given a dietary dose of 2000 mg/kg/day (approximately 630 times the maximum recommended daily oral dose in adults and in children based on a comparison of the AUCs of total drug exposure) of zafirlukast showed an increased incidence of urinary bladder transitional cell papillomas. Zafirlukast was not tumorigenic at dietary 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 AUC of total drug exposure) in mice and at dietary doses up to 400 mg/kg (approximately 550 times the maximum recommended daily oral dose in adults and in children based on a comparison of the AUCs of total drug exposure) in rats. 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 (an in vitro human peripheral blood lymphocyte clastogenic assay and a 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 daily oral dose in adults 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 (approximately 410 times the maximum recommended daily oral dose in adults on a mg/m^2 basis) 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 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 of ACCOLATE at doses of 10 mg twice daily has been demonstrated in 205 pediatric patients aged 5 through 11 years in placebo-controlled trials lasting up to six weeks and with 179 patients in this age range participating in 52 weeks of treatment in an open label extension

ACCOLATE® (zafirlukast) Tablets

The effectiveness of ACCOLATE for the prophylaxis and chronic treatment of asthma in pediatric patients aged 7 to 11 years is based on an extrapolation of the demonstrated efficacy of ACCOLATE in adults with asthma and the likelihood that the disease course, and pathophysiology and the drug's effect are substantially similar between the two populations. The recommended dose for the patients 7-11 years of age is based upon a cross-study comparison of the pharmacokinetics of zafirlukast in adults and pediatric subjects, and on the safety profile of zafirlukast in both adult and pediatric patients at doses equal to or higher than the recommended dose.

The effective dose of zafirlukast in pediatric patients 5 and 6 years of age has not yet been established. The safety and effectiveness of zafirlukast for pediatric patients less than 5 years of age has not been established.

Geriatric Use: Based on cross study comparison, the clearance of zafirlukast is reduced in patients 65 years of age and older such that C_{max} and AUC are approximately 2- to 3-fold greater than those of younger patients (see DOSAGE AND ADMINISTRATION, and CLINICAL PHARMACOLOGY sections).

A total of 8,094 patients were exposed to zafirlukast in North American and European short-term placebo-controlled clinical trials. Of these, 243 patients were elderly (age 65 years and older). No overall difference in adverse events was seen in the elderly patients, except for an increase in the frequency of infection among zafirlukast treated elderly patients compared to placebo treated elderly patients (7.0% vs. 2.9%). The infections were not severe, occurred mostly in the lower respiratory tract, and did not necessitate withdrawal of therapy.

An open-label, uncontrolled, 4-week trial of 3759 asthma patients compared the safety and efficacy of ACCOLATE 20 mg given twice daily in three patient age groups, adolescents (12-17 years), adults (18-65 years), and elderly (greater than 65 years). A higher percentage of elderly patients (n=384) reported adverse events when compared to adults and adolescents. These elderly patients showed less improvement in efficacy measures. In the elderly patients, adverse events occurring in greater than 1% of the population included headache (4.7%), diarrhea and nausea (1.8%), and pharyngitis (1.3%). The elderly reported the lowest percentage of infections of all three age groups in this study.

ADVERSE REACTIONS

Adults and Children 12 years of age and older

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. In clinical trials, most of these have been observed at doses four times higher than the recommended dose. The following hepatic events (which have occurred predominantly in females) have been reported from postmarketing adverse event surveillance of patients who have received the recommended dose of ACCOLATE (40 mg/day): cases of symptomatic hepatitis (with or without hyperbilirubinemia) without other attributable cause; and rarely, hyperbilirubinemia without other elevated liver function tests. In most, but not all, postmarketing reports, the patient's symptoms abated and the liver enzymes returned to normal or near normal after stopping ACCOLATE. In rare cases, patients have progressed to hepatic failure.

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, arthralgia and myalgia 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 two clinical drug interaction studies (see CLINICAL PHARMACOLOGY and PRECAUTIONS - Drug Interactions sections.)

Pediatric Patients 5 through 11 years of Age

ACCOLATE has been evaluated for safety in 788 pediatric patients 5 through 11 years of age. Cumulatively, 313 pediatric patients were treated with ACCOLATE 10 mg bid or higher for at least 6 months, and 113 of them were treated for one year or longer in clinical trials. The safety profile of ACCOLATE 10 mg twice daily-versus placebo in the 4 and 6-week double-blind trials was generally similar to that observed in the adult clinical trials with ACCOLATE 20 mg twice daily.

In pediatric patients receiving ACCOLATE in multi-dose clinical trials, the following events occurred with a frequency of ≥2% and more frequently than in pediatric patients who received placebo, regardless of causality assessment: headache (4.5 vs. 4.2%) and abdominal pain (2.8 vs. 2.3%).

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 on a mg/m^2 basis and approximately 300 times the maximum recommended daily oral dose in children on a mg/m^2 basis), 2000 mg/kg in rats (approximately 410 times the maximum recommended daily oral dose in adults on a mg/m^2 basis and approximately 600 times the maximum recommended daily oral dose in children on a mg/m^2 basis), and 500 mg/kg in dogs (approximately 340 times the maximum recommended daily oral dose in adults on a mg/m^2 basis and approximately 500 times the maximum recommended daily oral dose in children on a mg/m^2 basis).

Overdosage with ACCOLATE has been reported in four patients surviving reported doses as high as 200 mg. The predominant symptoms reported following ACCOLATE overdose were rash and upset stomach. There were no acute toxic effects in humans that could be consistently ascribed to the administration of ACCOLATE. 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

Adults and Children 12 years of age and older

The recommended dose of ACCOLATE is 20 mg twice daily in adults and children 12 years and older.

Pediatric Patients 7 through 11 years of Age

The recommended dose of ACCOLATE in children 7 through 11 years of age is 10 mg twice daily.

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.

HOW SUPPLIED

ACCOLATE 10 mg Tablets, (NDC 0310-0401) white, unflavored, round, biconvex, film-coated, mini-tablets identified with "ZENECA" debossed on one side and "ACCOLATE 10" debossed on the other side are supplied in opaque HDPE bottles of 60 tablets and hospital Unit Dose blister packages of 100 tablets.

ACCOLATE 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.

Rev N 06/00

ZENECA

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

24 PAGE(S) REDACTED

Draft

Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-547/S011

MEDICAL REVIEW(S)

JAN 2 8 2000

MEDICAL OFFICER REVIEW

Division Of Pulmonary And Allergy Drug Products (HFD-570)

APPLICATION #:	20-547	**APPLICATION TYPE:**	NDA supplement
SPONSOR:	Astra-Zeneca	**TRADE NAME:**	Accolate
CATEGORY:	LTD4 antagonist	**GENERIC NAME:**	zafirlukast
		ROUTE:	oral
MEDICAL OFFICER:	R. F. Anthracite	**REVIEW DATE:**	1/14/2000

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
8/10/99	8/11/99	supplement	geriatric labeling

RELATED APPLICATIONS (if applicable)

Document Date	Application Type	Comments
6/26/95	NDA submission	

REVIEW SUMMARY:

The ACCEPT uncontrolled open-label trial compared safety and efficacy of zafirlukast among over 3000 patients of three different age groups. The elderly, age > 65 years, had the most severe asthma, the smallest response to treatment by all of the eight efficacy measures employed, the most AE's, the most treatment-related AE's and the most serious AE's of all age groups. The original NDA safety data base of over 3000 people exposed to zafirlukast found increased infections in patients over the age of 55 years. The "infections" were comprised largely of respiratory complaints. In 1997 this data base was expanded to over 5000 patients exposed and a publication sponsored by Zeneca again identified "infections" in the elderly as more frequently seen with zafirlukast than with placebo. In this latter publication, the elderly were defined as having an age greater than 65 years. Both the original NDA and the subsequent 1997 publication found that the magnitude of increased "infections" in the elderly was a five-fold increase over placebo.

These data strongly suggest that the elderly have less efficacy and more untoward effects, hence, a reduced benefit/risk ratio compared with patients of ages younger than 65 years. The GERIATRIC USE section of the package insert should reflect this.

OUTSTANDING ISSUES:

- None.

RECOMMENDED REGULATORY ACTION

New Clinical Studies:	_____	**HOLD**	_____	**MAY PROCEED**
NDA/Efficacy/Label Supplements:	XXX	**APPROVABLE**	_____	**NOT APPROVABLE**

SIGNATURES

Reviewer: /S/ **Date:** 1/14/2000

Team Leader: /S/ **Date:** 1/28/2000

TABLE OF CONTENTS

I. EXECUTIVE SUMMARY

The ACCEPT trial was conducted to determine whether the response to zafirlukast treatment varied with age and, if so, to describe age-related differences. It was an uncontrolled, open-label, multi-center, four-week U.S. trial of zafirlukast, 20 mg twice daily on an empty stomach. Enrollment of 3759 safety-evaluable patients provided a large data base. Patients 12 years of age and older were eligible if they had symptoms of asthma within the preceding month, were candidates for chronic asthma therapy, had $FEV_{1.0}$'s 45-85% of predicted after > 4 hours of abstinence from beta-2 agonists and were non-smokers. Efficacy-evaluable patients numbered 3186 and were defined as having contributed all baseline and 7-days of post-treatment data. Subgroups of patient ages at trial entry were defined as "adolescent" (12-17 year of age), "adult" (18-65 years of age) and "elderly" (≥ 66 year of age).

The elderly age group had the highest frequency of asthma duration greater than 20 years and the most severe asthma by many measures. All four of the PFT endpoints and all four of the daily diary variables showed the smallest improvement in the elderly age group. A variety of methods were used to sort out the affects of age group and asthma severity on response to treatment. The weight of evidence seemed to be that age was a more important predictor of response, or lack of it, than was baseline disease severity. AE's occurred with increasing frequency in groups of increasing age, as did AE's deemed to be treatment-related. Serious AE's were also more frequent in the elderly group than in the adolescent or adult groups. The overall finding was that the benefit-risk ratio was lowest in patients ≥ 66 years of age.

At the time of the original NDA review, zafirlukast had been administered to over 3330 patients and over 500 of them had taken the drug for more than one year. Patients of age > 55 years were defined as the elderly group. "Infection" was the only AE with an increased frequency in zafirlukast-treated elderly patients compared with placebo and this was substantial (placebo = 3/104 = 2.9%; zafirlukast = 23/173 = 13.3%). The majority of the "infection" AE's described respiratory symptoms and the elderly showed greater infection frequency with longer treatment duration and with greater total milligrams of zafirlukast exposure. Age-related infections were also reported in an article retrieved by a MEDLINE search that was published in 1997 and sponsored by Zeneca. It reported on a more complete data base of 93 clinical trials involving 5188 subjects who took the medication, 662 treated for over 12 months. Patients over 65 years old (n=240) were again reported as showing an increased frequency of infections. These were usually mild and did not necessitate withdrawal from therapy (placebo = 1.4%; zafirlukast = 7.8%). Younger patients treated with zafirlukast did not report more "infection" AE's compared with placebo. Both of these publications, though using many patients in the same data base, reported a five-fold increase of infections in elderly patients treated with zafirlukast compared with placebo treatment. The elderly reported the fewest AE's of infection in the ACCEPT trial.

Taken together, these data should result in a change in the package insert. The GERIATRIC USE section should reflect a lesser potential benefit of zafirlukast to elderly patients as well as greater expected untoward side effects in this older age group.

/S/

Raymond F. Anthracite, M.D.
Medical Review Officer

cc:
NDA #20-547
HFD-570/Division Files
HFD-570/Medical Team Leader/Chowdhury
HFD-570/Medical Reviewer/Anthracite
HFD-570/PharmTox Reviewer/Sancilio
HFD-570/Chemistry Reviewer/Korshidi
HFD-570/ Project Manager/Jani

II. LABELING REVISION

GERIATRIC USE

Based on cross-study comparisons, the clearance of zafirlukast is reduced in patients 65 years and older such that Cmax and AUC are approximately 2- to 3-fold greater than those of younger patients (see DOSAGE AND ADMINISTRATION, clinical pharmacology sections).

APPEARS THIS WAY
ON ORIGINAL

III. THE EFFECT OF AGE ON RESPONSE TO ZAFIRLUKAST IN PATIENTS WITH ASTHMA IN THE ACCOLATE® CLINICAL EXPERIENCE AND PHARMACOEPIDEMIOLOGY TRIAL (ACCEPT)

III.A. SUMMARY

This trial was conducted to determine whether the response to zafirlukast treatment varied with age and, if so, to describe age-related differences. It was published in the Journal of Family Practice (1999; 48:425-432) but only a draft report was submitted with this supplement. This was an uncontrolled, open-label, multi-center, four-week U.S. trial of zafirlukast, 20 mg twice daily on an empty stomach. Efficacy variables were baseline and change from baseline measured twice daily by $FEV_{1.0}$ and PEFR, and once daily diary card assessments of beta-2 agonist use, asthma symptoms, nighttime awakening and morning asthma. Enrollment of 3759 safety-evaluable patients provided a large data base. Patients 12 years of age and older were eligible if they had symptoms of asthma within the preceding month, were candidates for prophylactic or chronic asthma therapy, had $FEV_{1.0}$'s 45-85% of predicted after > 4 hours of abstinence from beta-2 agonists and were non-smokers. Efficacy-evaluable patients numbered 3186 and were defined as having contributed all baseline and 7-days of post-treatment data. Subgroups of patient ages at trial entry were defined as "adolescent" (12-17 year of age), "adult" (18-65 years of age) and "elderly" (≥ 66 year of age).

This was overwhelmingly a study of Caucasians the majority of who were female or had moderate asthma. The elderly age group had the highest frequency of asthma duration > 20 years and of severe asthma. The elderly age group also had the lowest baseline mean PFT values and showed the smallest mean improvement from baseline for all four PFT endpoints. Two out of four of the baseline mean daily diary variables indicated that the elderly group was more symptomatic than the other two age groups. The elderly group had the highest baseline beta-2 agonist use and asthma symptom scores. All four of the daily diary variables showed the least improvement in the elderly age group. A variety of methods were used to sort out the affects of age group and asthma severity on response to treatment. The weight of evidence seemed to be that age was a more important predictor of response, or lack of it, than was baseline disease severity. AE's occurred with increasing frequency in groups of increasing age, as did AE's deemed to be treatment-related. Serious AE's were also more frequent in the elderly group than in the adolescent or adult groups. The overall finding was that the benefit-risk ratio was lowest in patients ≥ 66 years of age.

III.B. OBJECTIVE

This trial was conducted during 1996-7 and evaluated patients with varying degrees of asthma severity, differing concomitant asthma therapies who were treated by physicians of differing specialties. With an enrollment of over 3700 patients, it is the largest clinical trial of this drug to date. The point of the trial was to determine whether the response to zafirlukast treatment varied with age and, if so, to describe age-related differences [Tab 1:4-5].

III.C. PROTOCOL

This was an uncontrolled, open-label, multi-center, four-week U.S. trial. It began with a three-day run-in period during which baseline pulmonary function data were obtained and diary card assessments were performed. At the baseline or screening visit, patients provided a medical and smoking history and underwent a complete physical examination. Each patient received an ——— Airway Monitor System and performed baseline pulmonary function tests (PFT's); e.g., $FEV_{1.0}$. Patients recorded overall asthma symptoms, nighttime awakenings, morning asthma symptoms and beta-2 agonist use on daily diary cards.

This run-in was followed by four weeks of treatment of all patients with zafirlukast 20 mg BID. Domiciliary PFT's were performed twice daily with the ——— once in the morning before beta-2 agonist use and once again 12 hours later. Daily diary cards were used to capture overall asthma symptoms, nighttime awakenings, morning asthma symptoms and beta-2 agonist use as in the baseline period. There were three formal visits, one at baseline or screening and two more after the second and fourth weeks of treatment. Patient compliance, response to treatment and adverse events (AE's) were assessed at weeks 2 and 4 [Tab 1:5-6].

III.D. PATIENTS

Patients 12 years of age and older were eligible if they had symptoms of asthma within the preceding month, were candidates for prophylactic or chronic asthma therapy, had $FEV_{1.0}$'s 45-85% of predicted after > 4 hours of abstinence from beta-2 agonists and were non-smokers. This last was defined as ≥ 6 months of tobacco abstinence and a total smoking history of ≤ 10 pack-years. Patients had to have been on a stable regimen of asthma medications for 4 weeks prior to entry. Exclusion criteria were: any chronic lung or airway problem other than asthma; acute asthma exacerbation at the time of screening; treatment with oral corticosteroids for > 10 days within 4 weeks of screening; known active hepatic dysfunction; current treatment with beta-blockers or warfarin; participation in an investigational drug trial within 30 days; and, pregnant or lactating females [Tab 1:7].

The "efficacy evaluable" patient sample was more restrictively defined than the usual modified intent-to-treat sample that we see and met the following criteria:

- received ≥ 7 consecutive days of medication
- had 3 days of baseline and 7 consecutive days of post-baseline pulmonary function data (i.e., morning and evening PEFR and morning and evening $FEV_{1.0}$) obtained by ——— device
- had a completed CRF including one week of asthma scores

The safety data base consisted of all enrolled patients [Tab 1:6, 9].

Subgroups of patient ages at trial entry were defined as adolescent (12-17 year of age), adult (18-65 years of age) and elderly (≥ 66 year of age). The characteristic and subgroup defined by asthma severity at entry was determined by the 1991 National Heart Lung and Blood Institute guidelines (NIH publication no. 91-3042, Page 10, Figure 1-5). [Tab 1:8-9].

III.E. TREATMENT

Accolate was given as one 20 mg tablet BID on an empty stomach; i.e., excluding the time interval from one hour before through two hours after meals. All prescription and non-prescription medications were allowed as long as they had not been stopped or started within 4 weeks of screening. Modification of dosage, substitutions and additions of any asthma medication were "discouraged" [Tab 1:6]. No information on formulation, batch or lot was provided, but this presumably was the marketed formulation.

III.F. PARAMETERS

The trial was said to be powered to evaluate subgroups with a minimum of 100 patients. Eight variables were evaluated for efficacy: morning and evening PEFR; morning and evening $FEV_{1.0}$; asthma symptom score, number of nighttime awakenings, number of mornings with asthma symptoms; and, beta-2 agonist use. The asthma symptom score was a four-point scale (0 = no symptoms, 1 = mild symptoms that did not interfere with activity, 2 = moderate symptoms that interfered with some activities, 3 = severe symptoms that interfered with many activities). Nighttime awakenings, and presumably mornings with asthma; were recorded once daily as "yes" or "no." Beta-2 agonist use was scored as the number of puffs per day [Tab 1:5-6, Tab 2:Methods section]. There was no way to determine if the metrics of these endpoints and the comparisons among them had been prospectively specified. Details of sample size determinations were not given and it was not clear if significance testing was one- or two-tailed. Comparisons were not specifically done under "protection" of a significant 'F' statistic and correction of the Type I Error for multiple comparisons was not addressed. Finally, least squares (LS) mean change from baseline was based on undefined and unknown numbers of covariates. For all of these reasons, Type I Error probabilities will not be reported for this study because they would contribute more to confusion than to clarity.

Safety variables included proportions of patients with each AE and "asthma worsening" that was defined by 25% reduction in pulmonary function (*sic*), an increase in

asthma symptoms associated with an increase in the dose of any concomitant asthma medication or with the addition of an asthma medication [Tab 1:9-10].

III.G. DEMOGRAPHICS

Eighty-three percent (3120) of the 3759 patients enrolled in this trial completed the four weeks of treatment and 3207 of those enrolled met the efficacy evaluable criteria. Twenty-one of the efficacy evaluable patients had no age data and were excluded from the efficacy analysis leaving 84.8% (3186) of those enrolled as efficacy evaluable patients.

This was overwhelmingly a study of Caucasians the majority of who were female or had moderate asthma (shaded cells in table below). The elderly age group had the highest frequency of asthma duration > 20 years and of severe asthma. In an apparent contradiction to the last finding, the elderly also reported the lowest frequency of ER visits for treatment of asthma in the preceding year, and were no more frequently hospitalized during the preceding year than patients in the other age categories [Tab 1:10-11, 24-6].

BASELINE DEMOGRAPHIC CHARACTERISTICS FOR EFFICACY EVALUABLE PATIENTS, N (%) [Tab1:24-6]			
Characteristic	**Adolescents (n=263)**	**Adults (n=2602)**	**Elderly (n=321)**
SEX			
male	143 (54)	850 (33)	127 (40)
female	120 (46)	1750 (67)	194 (60)
NR*	0 (0)	2 (< 1)	0 (0)
RACE			
white	220 (84)	2206 (85)	281 (88)
black	18 (7)	183 (7)	14 (4)
hispanic	15 (6)	141 (5)	13 (4)
other/NR*	10 (4)	70 (3)	13 (4)
ASTHMA DURATION (y)			
≤ 20	261 (99)	1632 (63)	188 (59)
> 20	0 (0)	960 (37)	131 (41)
NR*	2 (< 1)	10 (< 1)	2 (< 1)
ASTHMA SEVERITY			
mild	40 (15)	293 (11)	27 (8)
moderate	178 (68)	1745 (67)	193 (61)
severe	42 (16)	507 (19)	94 (29)
NR*	3 (1)	57 (2)	4 (1)
MEAN FEV 1.0 (% pred)	75.5	74.2	73.8
ER visit in last year	77 (29)	680 (26)	53 (17)
Hospitalized in last year	39 (15)	308 (12)	38 (12)
PREVIOUS TREATMENT			
SAB2*	56 (21)	486 (19)	44 (14)
NS*+SAB2	37 (14)	295 (11)	39 (12)
ICS*+SAB2	70 (27)	624 (24)	76 (24)
SAB2+NS+ICS	100 (38)	1197 (46)	162 (50)

*NR = not recorded SAB2 = short-acting inhaled beta-2 agonist ICS = inhaled corticosteroid
NS = oral beta-2 agonist, mast cell stabilizer, xanthine or long-acting inhaled beta-2 agonist

III.H. EFFICACY

III.H.1. PULMONARY FUNCTION VARIABLES

Baseline and change from baseline to week #4, the latter presented as LS mean change, are presented in the table below. Data analyses followed the last-value carried forward convention and were somewhat surprising because the largest sum of patients in all three age groups for any of the pulmonary function variables was 2783, which is 403 patients less than the 3186 efficacy evaluable patients in the trial [Tab 1:9].

CHANGE IN PULMONARY FUNCTION VARIABLES FROM BASELINE TO WEEK #4 IN EFFICACY EVALUABLE PATIENTS, mean (SD or SE) [Tab 1:27]

Measure	Age Group		
	n Adolescents	n Adults	n Elderly
AM PEFR (L/min)	218	2250	263
Baseline (SD)	353.1 (100.8)	357.5 (112.5)	265.1 (111.3)
LS change (SE)	45.3 (5.9)	35.8 (1.8)	14.6 (5.5)
PM PEFR (L/min)	234	2285	264
Baseline (SD)	379.7 (93.8)	375.9 (112.8)	280.8 (105.6)
LS change (SE)	41.0 (5.9)	31.4 (1.9)	10.8 (5.7)
AM FEV 1.0 (L)	218	2250	263
Baseline (SD)	2.59 (0.87)	2.34 (0.89)	1.55 (0.65)
LS change (SE)	0.35 (0.06)	0.22 (0.02)	0.07 (0.05)
PM FEV 1.0 (L)	234	2285	264
Baseline (SD)	2.72 (0.86)	2.41 (0.86)	1.62 ((0.64)
LS change (SE)	0.39 (0.05)	0.21 (0.02)	0.06 (0.05)

When the LS mean change from baseline for each of the four efficacy endpoints was viewed as a function of ascending age category, there was an inverse relationship; the older the group, the smaller the LS mean change from baseline. The elderly age group had the lowest baseline mean values for each of the four pulmonary function efficacy endpoints, about 75% of the baseline means of the other two groups, and the smallest LS mean change from baseline to week #4, about 35% of the LS mean change in the other two groups. Proportional to the other two groups, the elderly had a relatively lesser improvement than it did a lesser baseline.

III.H.2. DAILY DIARY VARIABLES

The four variables evaluated by diary card are presented in the table below and show about the same number of missing persons as did the pulmonary function endpoints; data from 2778 patients were presented, which is 408 patients less than the 3186 expected.

CHANGE IN DAILY DIARY CARD VARIABLES FROM BASELINE TO WEEK #4 IN EFFICACY EVALUABLE PATIENTS, mean (SD or SE) [Tab 1:28]			
Measure	Age Group		
	Adolescents n = 224	Adults n = 2263	Elderly n = 291
Beta-2 Agonist (puffs/day)			
Baseline (SD)	4.49 (4.39)	6.12 (5.17)	6.21 (5.55)
LS change (SE)	-1.72 (0.21)	-1.52 (0.07)	-0.59 (0.19)
Asthma Symptoms (0-3)			
Baseline (SD)	7.86 (4.71)	8.88 (4.58)	9.35 (4.55)
LS change (SE)	-3.12 (0.27)	-2.67 (0.08)	-2.18 (0.23)
Night Awakening (#/week)			
Baseline (SD)	1.37 (2.17)	2.03 (2.61)	1.61 (2.56)
LS change (SE)	-0.85 (0.11)	-0.94 (0.04)	-0.74 (0.10)
AM with Asthma (#/week)			
Baseline (SD)	2.97 (2.77)	4.02 (2.87)	3.45 (2.98)
LS change (SE)	-1.94 (0.16)	-1.50 (0.05)	-1.32 (0.14)

Some of the baseline mean data indicated that the elderly group was more symptomatic than the other two age groups. The elderly showed higher baseline beta-2 agonist use and asthma symptom scores. All four of the diary variables showed that improvement was least in the elderly age group. The elderly showed the smallest LS mean reductions in beta-2 agonist use, asthma symptom scores, nighttime awakenings and mornings with asthma.

III.H.3. AGE-SEVERITY INTERACTIONS

The sponsor attempted to sort out response to treatment by age group and by asthma severity. Dichotomous, arbitrary and undoubtedly post-hoc categories of responders and non-responders were derived from changes in $FEV_{1.0}$, PEFR and asthma symptom scores. They concluded that asthma severity did not affect the numbers of patients in any age group who "responded" in terms of PFT's. When categorization was determined by asthma symptom scores, the more severe the asthma the greater percentage of patients "responded" in the elderly sub-group [Tab 1:13, 29]. Somewhat at odds with this latter interpretation, an ANCOVA model showed no age-by-disease severity interaction, as tested by $p < 0.10$, and severity was abandoned as a covariate but age was kept in the model [Tab 1:9]. One interpretation of these data, and the information previously reviewed, is that age was a more important predictor of response, or lack of it, than was disease severity.

III.I. SAFETY

Patients reporting AE's occurred with increasing frequency in groups of increasing age, as did patients reporting AE's deemed to be treatment-related. Patients reporting serious AE's were also most frequent in the elderly group, compared with the adolescent and adult groups, but none were considered to be treatment-related.

PERCENTAGES OF PATIENTS WITH AE's ACROSS AGE GROUPS [Tab 1:14]			
Type of Adverse Event	Age Groups*		
	Adolescents (n = 312)	Adults (n = 3021)	Elderly (n = 384)
Any AE	11.5	17.5	18.8
Treatment-Related AE's	4.2	7.4	8.1
Serious AE's	1.6	0.9	2.3
Treatment-Related SAE's	0.0	0.0	0.0
*Excludes 42 patients whose age category was unknown			

When the most common AE's were analyzed by age group, the elderly had the greatest percentage of headache, abdominal pain, diarrhea and nausea, and the lowest frequency of infection and sinusitis, but absolute numbers of AE's in two of the groups were small [Tab 1:14, 31].

AE's OCCURRING IN ≥ 1% OF PATIENTS ACROSS AGE GROUPS, REGARDLESS OF ATTRIBUTION, n (%) [Tab 1:14, 31]			
Adverse Event	Age Groups*		
	Adolescents (n = 312)	Adults (n = 3021)	Elderly (n = 384)
headache	11 (3.5)	109 (3.6)	18 (4.7)
infection	4 (1.3)	19 (0.6)	1 (0.3)
abdominal pain	0 (0)	8 (0.3)	4 (1.0)
diarrhea	3 (1.0)	24 (0.8)	7 (1.8)
nausea	2 (0.6)	45 (1.5)	7 (1.8)
pharyngitis	4 (1.3)	42 (1.4)	5 (1.3)
sinusitis	3 (1.0)	38 (1.3)	1 (0.3)
*Excludes 42 patients whose age category was unknown			

Although compliance was said to have been monitored, I could find no mention of it in the draft report nor in the journal article.

APPEARS THIS WAY
ON ORIGINAL

IV. ADVERSE EVENT DATA FROM ORIGINAL NDA

IV.A. SUMMARY

At the time of this report, zafirlukast had been administered to over 3330 patients and over 500 of them had taken the drug for more than one year. This analysis defined age > 55 years as the elderly group, which included some younger patients than the current regulatory definition of elderly, age ≥ 65 years [21 CFR 201.57(f)(10)]. Placebo-controlled studies showed that "Infection" was the only AE with an increased frequency in zafirlukast-treated patients whose age was greater than 55 years. This was investigated further by analysis of placebo-controlled trials of comparable duration. The interaction was confirmed and appeared substantial (placebo = 3/104 = 2.9%; zafirlukast = 23/173 = 13.3%). The elderly showed greater infection frequency with longer treatment duration and with greater total zafirlukast exposure, in milligrams. Age-related infections could not be attributed to a diminution, or low absolute number of inflammatory cells in the peripheral blood. In the over-age-55 group, "infection" overwhelmingly described respiratory symptoms, sometimes represented as asthma exacerbations. Open-label trials did not confirm the suppositions that infections in the elderly: 1)were restricted to patients exposed to corticosteroid co-administration; or, 2)were an epiphenomenon of an abnormally low frequency of infections in placebo groups.

IV.B. PLACEBO-CONTROLLED TRIALS

At the time of this report, zafirlukast had been administered to over 3330 patients and over 500 of them had taken the drug for more than one year. Three age ranges were defined for all trials: age < 18 years; 18 ≤ age ≤ 55 years; and, age > 55 years. "Infection" was the only AE which showed an increased frequency in zafirlukast-treated patients and subject age > 55 years. This was investigated further by analysis of placebo-controlled trials of comparable duration. The interaction was confirmed and appeared substantial (placebo = 3/104 = 2.9%; zafirlukast = 23/173 = 13.3%). One patient over the age of 55, had a serious AE, appendicitis, and was withdrawn after undergoing an appendectomy [6/26/95 ISS 109:259-61]. Eighty-two percent (24/29) of the AE's mapped to the COSTART term "infection," for zafirlukast patients > 55 years of age, included: chest infection; lower respiratory tract infection; chest cold; wheezy cough and pale green sputum; infection; fever; cough; and, more asthma. The sponsor noted that three trials involving the use of corticosteroids were disproportionately represented among older patients with infection. In these corticosteroid trials, the proportion of patients older than 55 years with infection was higher in the zafirlukast-treated patients, than in patients who received placebo [6/26/95 ISS 109:262-5].

Proportionality of several dose-related variables to the frequency of "infection" was sought and these variables were: daily dose; total exposure; and, duration of treatment [CANDA; Data Review; Accolate; 4-Month UPDT; Analysis/Reporting; Data Set = ADVERSEV; Analysis Program = AE's by Dose - Placebo, (AE's) By Exposure - Placebo, AE's by (duration of treatment) and Trial Group; Selection Variable = Age Entry (grouped); Selection Value > 55].

FREQUENCY OF AE = "INFECTION" IN PATIENTS > 55 YEARS OF AGE: RELATION TO DAILY DOSE, TOTAL EXPOSURE AND DURATION OF EXPOSURE TO ZAFIRLUKAST [CANDA Tables T3.5.1, A10.4.3 and A10.5.1 corrected in 3/21/96 FAX]					
Daily Dose (mg)	< 40 (n = 54)	= 40 (n = 198)	> 40 (n = 61)		
	4 (7.4)*	17 (8.6)	5 (8.2)		
Total Exposure** (mg)	<= 1000 (n = 313)	1000< & ≤ 3500 (n = 236)	3500 < & ≤ 16000 (n = 132)		
	11 (3.5)	9 (3.8)	10 (7.6)		
Duration** (weeks)	≤ 1 (n = 313)	1 < & ≤ 4 (n = 280)	4 < & ≤ 8 (n = 244)	8 < & ≤ 20 (n = 178)	> 20 (n = 21)
	3 (1.0)	7 (2.5)	7 (3.9)	15 (8.4)	0 (0.0)
* All data are presented as "mean (%)"					
** Groups are not necessarily mutually exclusive for these measures					

The daily dose showed no evidence of dose-proportionality with the frequency of infection. A relation between duration of treatment and infection frequency was present, as was a relation between infection frequency and total zafirlukast exposure, in milligrams.

Various demographic characteristics were compared between zafirlukast and placebo groups in the age-greater-than-55 subset [CANDA; Data Review; 4-Month UPDT; Analysis/Reporting; Data Set = ADVERSEV; Analysis Program = AE's in Patients - Placebo; with Saved Subsets: Age Entry (grouped) > 55; Race = Caucasian, Black, Other; or, Sex = Male or Female].

AE = "INFECTION" IN EACH TREATMENT GROUP WHERE AGE > 55 YEAR FOR CERTAIN DEMOGRAPHIC SUBSETS [CANDA Table T3.2.1]				
Demographic Characteristic	Zafirlukast		Placebo	
	N	Patients (%)	N	Patients (%)
Caucasian	264	22 (8.3)	134	4 (2.9)
Black	6	0 (0.0)	2	0 (0.0)
Other	14	1 (7.1)	5	0 (0.0)
Male	165	13 (7.9)	89	4 (4.5)
Female	148	10 (6.8)	86	0 (0.0)

Increased "infection" in patients over the age of 55 years seemed to be restricted to Caucasians, who comprised 82.4% of the placebo-controlled trial safety data base.

A reduction in the number of inflammatory cells was a possible concomitant of infection, so mean counts of inflammatory cells were examined for all patients over the age of 55 years in both zafirlukast and placebo groups. The following reviewer-synthesized table shows the white blood cell, neutrophil and lymphocyte counts of the two treatments, for the older age group [CANDA; Data Review; Accolate; 4-Month UPDT; Analysis/Reporting; Data Set = N_WBC, N_NEUT, N_LYMPHS; Analysis Program = Mean Labs BEF/END TRT; ± Saved Subsets: Selection Variable = Age Entry (grouped) <18, 18-55, >55].

BASELINE AND END-OF-TREATMENT CHANGE IN WHITE BLOOD CELL COUNT, NEUTROPHILS AND LYMPHOCYTES FOR EACH TREATMENT GROUP, OVER 55 YEARS OF AGE
(all trials, excluding long-term, open-label studies)

	Zafirlukast: mean (S.D.)			Placebo: mean (S.D.)		
Cell Type	n	Before Treatment	Change - End of Treatment	n	Before Treatment	Change - End of Treatment
WBC ($x10^9$/L)	308	6.64 (1.63)	-0.01 (1.45)	168	6.39 (1.60)	0.12 (1.48)
Neutrophils (%)	199	59.55 (9.39)	-1.31 (8.91)	126	57.48 (8.17)	-0.66 (8.06)
Lymphs (%)	200	29.31 (8.40)	0.81 (7.21)	126	30.17 (7.35)	-0.06 (6.74)

Both white blood cell count and percent-neutrophils showed a mean decline, from baseline to end of treatment, that was more apparent in the zafirlukast group than in the placebo group. Though the mean white blood cell count and percent neutrophils were both greater at the end of treatment in the zafirlukast group than in the placebo group and the magnitude of the changes from baseline were not impressive, these findings did at least permit the possibility of a large change in a small subgroup of patients. Therefore, shift tables for all three cellular elements in the older age group were developed [CANDA; Data Review; Accolate; 4-Month UPDT; Analysis/Reporting; Data Set = N_WBC, N_NEUT, N_LYMPHS; Analysis Program = Lab Ranges BEF/END Treatment; Selection Variable = Age Entry (grouped) = <18, 18 to 55, >55]. These tables did not reveal an age-related diminution in any of these cellular elements that was more apparent in the zafirlukast than in the placebo treatment groups. Another analysis examined the frequency of infections in patients with lowest neutrophil counts of less than 40% [CANDA; Data Review; Accolate; 4-Month UPDT; Analysis/Reporting; Data Set = ADVERSEV; Analysis Program = AE's in Patients - Placebo; ± Saved Subset: Selection Variable = Min During TRT Value; Selection Value = < 40]. This was no more revealing than other attempts to define the issue of increased infection in terms of reductions in, or low values of, the number of various inflammatory cells.

From these analyses it is apparent that age-related infections could not easily be attributed to a diminution, or low absolute number of inflammatory cells. In the over-age-55 group, "Infection" was not confirmed by bacteriologic isolation and overwhelmingly described respiratory symptoms, sometimes represented as asthma

exacerbations. None of these satisfactorily explain the increased frequency of infection, in the zafirlukast group relative to the placebo group.

IV.C. OPEN-LABEL TRIALS

The previous association between age > 55 years and apparently greater frequency of the AE "infection" was examined in open-label trials [CANDA, Data Review; Accolate; 4 MO UPDT O-L; Analysis/Reporting; Data Set = ADVERSEV; Analysis Program = Adverse Events -- Total; (run)/Selection Variable = Age at D-B (grouped); Selection Value > 55/ <18 or 18 to 55].

PATIENTS REPORTING AE = "Infection" DURING OPEN-LABEL TRIALS
(4-Month Safety Update, open-label trials) [CANDA Table T3.2.4.3]

Category			At Risk	Number (%)
AGE	≤ 55 years		816	80 (9.8%)
	> 55 years		130	23 (17.7%)
	SEX (Age > 55)	Males	65	9 (13.8%)
		Females	65	14 (21.5%)
TOTAL (all ages)			946	118 (12.5%)

All patients > 55 years of age who reported infections were Caucasian, a racial group that represented 90.4% of all patients in this data base. There was an excess of females over males reporting this AE despite their equal representation in this subset of age. The daily dose of zafirlukast in the open-label extensions was almost universally 40 mg/day and no method was found to subset infections in various age categories by total milligrams of zafirlukast exposure. For these reasons, the previously noted dose-proportional nature of this association between age and infection could not be analyzed.

Also, the CANDA was not configured to easily query the possible relation between age/infection and corticosteroid medication. However, the previous supposition that infections in the elderly were restricted to studies with mandated corticosteroid co-medication was not supported. Similarly, the contention that infections in the elderly were an epiphenomenon of an abnormally low frequency of infections in the placebo group is not supported by the open-label extension trials. Infection in the elderly appeared to be a real problem that may be linked to greater bioavailability of the drug in the older age group.

V. LITERATURE SEARCH

V.A. SEARCH STRATEGIES AND RESULTS

"Accolate and over-65" resulted in 53 retrieved documents dated from March 1995 to May 1999. The abstracts and titles of these did not suggest that they offered any new information. "Accolate and elderly" retrieved 10 documents and one of these seemed to offer some new information [Tab 4:all pages (unnumbered)].

Barnes NC, Clinical tolerability of zafirlukast a new oral antileukotriene drug (Review, 16 refs), European Respiratory Review 1998; 8(54):194-198. Proceedings of a symposia sponsored by Zeneca Pharmaceuticals, Berlin, Sept. 1997.

PERTINENT PARTS OF THE ABSTRACT -- This paper reviews the safety of Accolate (zafirlukast) in 93 clinical trials involving 5188 subjects taking the medication vs 2573 subjects taking placebo. Accolate has been studied at doses of 20-40 mg BID and at up to 320 mg/day. Of these subjects, 1707 were treated with Accolate for at least 6 months, and 662 were treated for over 12 months. Ninety-two percent of the patients were 18 to 65 years old, with a mean age of 36 years....For patients over 65 years old (240), there was an increased incidence of infections which were usually mild and did not necessitate withdrawal from therapy (placebo = 1.4%; zafirlukast = 7.8%). For patients 18 to 64 years old (7156), there was no increased incidence of mild infection. For patients 12 to 18 years old (346), there was a lower incidence of mild infections (1.8% Accolate vs 4.9% placebo).....

VI. SPONTANEOUS ADVERSE EVENT REPORTS

A report dated 13 April 1999 captured spontaneous AE cases for three age categories, 12-18 years, 18-64 years and > 64 years. The AE's reported included:

1. bleeding/bruising
2. Churg Strauss
3. eosinophilia
4. liver events
5. myalgia/arthralgia
6. vasculitis

Conspicuously absent, was a tabulation by age of "infections." Of the six AE's above, only the AE "eosinophilia" was reported by a slightly greater percentage of the elderly than of the other age groups [Tab 6:1-2].

TOTAL PATIENT COUNTS FOR ACCOLATE EXCLUDING NON-REPORTABLE EVENTS [Tab 6:1-2]				
AE	Age Group	Total Patients With AE	Total Patients In Age Group	% Of Age Group
Eosinophilia	12 to <18	4	74	5.4
	18 to 64	56	864	6.5
	64+	24	328	7.3
	Unknown	6	385	1.6

A breakdown of the AE's falling under the group term, "eosinophilia," failed to show an overwhelming report count for the elderly for any of them. The elderly did show a greater frequency of "cellulitis" and of "pruritic rash" than younger age groups, but absolute numbers were small [Tab 6:3].

TEAM LEADER MEMORANDUM

DATE: January 26, 2000

TO: NDA 20-547

/S/ 1/28/2000

FROM: Badrul A. Chowdhury, MD, PhD
Acting Medical Team Leader,
Division of Pulmonary and Allergy Drug Products, HFD-570

SUBJECT: Secondary medical review of zafirlukast (Accolate®) geriatric supplement

CC: HFD-570: Meyer, Anthracite, Jani,

Administrative

NDA 20-547/SLR-011 geriatric labeling supplement for zafirlukast was submitted by Zeneca Pharmaceuticals on August 10, 1999. The goal date for completion of this application review is February 6, 2000. Zafirlukast was approved for prophylaxis and chronic treatment of asthma in patients 12 years of age and older on September 26, 1996. The age of approval was reduced down to 7 years on September 17, 1999. The recommended dose for patients 12 years and older is 20 mg by mouth BID, and for patients 7 to 11 years is 10 mg by mouth BID. The sponsor now submits this application in accordance to 21 CFR 201.57 (f) (10) regulation, which requires the addition of "Geriatric Use" subsection to the "PRECAUTIONS' section of prescription drug product labeling. For this submission, Zeneca has reviewed all information available that is relevant to the appropriate use of zafirlukast in elderly patients. Draft labeling revisions containing a new "Geriatric Use" subsection is also included. In subsequent sections, Zaneca's submitted documents are briefly reviewed. Detail review of the submission can be found in Dr. Anthracite's excellent medical review.

Justification documents submitted by Zeneca

The sponsor has submitted various documents in support of the labeling supplement. These include (1) a report and published article of a study titled "Zafirlukast in Clinical Practice: Results of the Accolate Clinical Experience and Pharmacoedidemiology Trial (ACCPET) in Patients with Asthma, (2) documents used to support approval of labeling for zafirlukast in the European Union, (3) review of current literature on the use of zafirlukast in the elderly, (4) post-marketing adverse events for zafirlukast from Zeneca's international data base, and [redacted]. Some of the pertinent results from these documents are summarized below.

ACCEPT trial was conducted to determine whether the response to zafirlukast treatment varied with age. This trial was published in the Journal of Family Practice (1999; 48:425-432). The published article and a brief draft trial report were submitted with this application.

ACCEPT was an uncontrolled, open-label, multi-center, US trial. The trial had a 3-day baseline period, and 4-week active treatment period during which patients were treated with zafirlukast 20 mg given on empty stomach twice daily. Domicilary PFT's were performed twice daily with ——— before beta-2 agonist use in the morning and again 12 hours later. Daily diary cards were used to capture asthma symptoms (0-4 scale), nighttime awakenings (yes or no), morning asthma symptoms (yes or no), and beta-2 agonist use. There were four clinic visits, one at baseline, and two more after the second and fourth weeks of treatment. Patients 12 years of age and older were eligible if they had symptoms of asthma within the preceding month, were candidates for chronic asthma therapy, had FEV_1 45-85% predicted after >4 hours abstinence from beta-2 agonist, and were non-smokers. Subgroup of patient ages at entry were defined as "adolescent" (12-17 years), "adult" (18-65 years), and "elderly" (≥66 years). A total of 3,186 patients were identified as efficacy evaluable, defined as having contributed to all baseline and 7-days of post-treatment data. The number of safety evaluable patients in the trial was 3,759. With this large enrollment, this is the largest zafirlukast clinical trial to date.

The patients enrolled in the in the trial were overwhelmingly Caucasians and of female sex. Among the elderly age category, 88% patients were Caucasians, and 60% were female. The elderly patients had the highest frequency of asthma duration at >20 years, had more severe asthma, and were more symptomatic at baseline as shown in Table 1. The elderly had the smallest mean improvement from baseline for all efficacy measures as compared to the adults and adolescents (Table 1). A variety of methods were used to sort out the effects of age and asthma severity on response to treatment. The weight of evidence suggests that age was more important predictor of response, than was baseline disease severity.

Adverse events occurred with increasing frequency with increasing age, as did adverse events deemed to be treatment-related (Table 2). Serious adverse events were also more frequent in the elderly group than in the other two age groups. When adverse events were analyzed by age groups, the elderly had the greatest percentage of headache, abdominal pain, diarrhea, and nausea, and lowest frequency of infection, and sinusitis. The absolute number of adverse events in the age groups was small.

Overall, this trial suggests that the benefit-risk ratio is lowest in patients ≥66 years of age.

Table 1. Change in efficacy variables from baseline to week 4*

Measure	Age Group		
	Adolescents (n = 218 to234)	Adults (n = 2250 to 2285)	Elderly (n = 263 to 291)
Morning FEV_1 (L)	2.59 → 0.35	2.34 → 0.22	1.55 → 0.07
Evening FEV_1 (L)	2.72 → 0.39	2.41 → 0.21	1.62 → 0.06
Morning PEFR (L/min)	353.1 → 45.3	357.5 → 35.8	265.1 → 14.6
Evening PEFR (L/min)	379.7 → 41.0	375.9 → 31.4	280.8 → 10.8

Measure	Age Group		
	Adolescents (n = 218 to234)	Adults (n = 2250 to 2285)	Elderly (n = 263 to 291)
Asthma symptom score	7.86 → -3.12	8.88 → -2.67	9.35 → -2.18
Beta-agonist use (puffs/day)	4.49 → -1.72	6.12 → -1.52	6.21 → -0.59
Nighttime awakening (#/wk)	1.37 → -0.85	2.03 → -0.94	1.61 → -0.74
Morning with asthma (#/wk)	2.97 → -1.94	4.02 → -1.50	3.45 → -1.32
* Reported as: baseline mean → LS mean change, significant difference from baseline to week 4 are shaded			
Source: Tab 1, page 27, 28			

Table 2. Adverse events

	Age Group		
	Adolescents (n = 312)	Adults (n = 3021)	Elderly (n = 384)
Type of adverse event, %			
Any AE	11.5	17.5	18.8
Treatment related AE	4.2	7.4	8.1
Serious AE	1.6	0.9	2.3
Treatment related SAE	0.0	0.0	0.0
Adverse events occurring in ≥1% of patients, n (%)			
Headache	11 (3.5)	109 (3.6)	18 (4.7)
Infection	4 (1.3)	19 (0.6)	1 (0.3)
Abdominal pain	0 (0)	8 (0.3)	4 (1.0)
Diarrhea	3 (1.0)	24 (0.8)	7 (1.8)
Nausea	2 (0.6)	45 (1.5)	7 (1.8)
Pharyngitis	4 (1.3)	42 (1.4)	5 (1.3)
Sinusitis	3 (1.0)	38 (1.3)	1 (0.3)
Source: Tab 1, page 14, 31			

Documents to support approval of labeling for zafirlukast in the European Union contains safety data from North American and European trials. No efficacy data is included in this submission. Demographics of the patients included in the submission are shown in Table 3. Number of patients above 65 years in the short-term placebo-controlled trials was 243. Incidence of adverse events in the short-term trials apparently increased with age, the overall rates of increase were similar for placebo and zafirlukast (Table 4). The most commonly reported adverse events were aggravated asthma, pharyngitis, headache, infection, and increased cough. Infection in the elderly patients appeared to be more common in those treated with zafirlukast compared with placebo (7% vs 2.9% of patients). The majority of the infections (15 out of 17) was of the lower respiratory tract, and was not severe. There was no death in elderly patients receiving zafirlukast (Tab 3 of the submission).

Trial 9188 was one of the trials in the above submission in which single-dose pharmacokinetics of zafirlukast was studied in elderly patients and compared to young patients. Mean Cmax and AUC were more than twice as high in the elderly as compared to the young adults, and the mean terminal half-life was longer. This information is incorporated in the current label in the CLINICAL PHARMACLOGY - "Clinical Pharmacokinetics and Bioavailability" section (Tab 3 of the submission).

Table 3. Demographics of subjects exposed to zafirlukast in North American and European trials*

	Short-Term Trials		Long-Term Trials (at 20 mg BID)
	Zafirlukast	Placebo	Zafirlukast
Number of trials	107	75	8
Subjects exposed	8094	3922	1242
Age, mean (range)	34.9 (5-79)	34.7 (5-77)	37.9 (12-76)
Age distribution, n (%)			
5 to 11 years	270 (3.3)	130 (3.3)	0 (0.0)
12 to <18 years	564 (7.0)	260 (6.6)	98 (7.9)
18 to 64 years	7017 (86.7)	3429 (87.4)	1099 (88.5)
>65 years	243 (3.0)	103 (2.6)	45 (3.6)
* Reported as: baseline mean → LS mean change, significant difference from baseline to week 4 are shaded			
Source: Tab 3 of the submission			

Table 4. Adverse events by age category in short-term trials

	Age Groups					
	12-17 years		18-64 years		>65 years	
	Zafirlukast (n = 564)	Placebo (n = 260)	Zafirlukast (n = 7017)	Placebo (n = 3429)	Zafirlukast (n = 243)	Placebo (n = 103)
Type of adverse event, %						
Any AE	37.8	47.7	48.7	48.1	52.7	50.5
AE with withdrawal	1.1	1.5	2.5	3.3	4.1	8.7
Serious AE	1.2	1.2	1.2	1.1	2.1	1.0
SAE with withdrawal	0.7	0.4	0.6	0.6	1.2	1.0
Adverse events occurring ≥3% of patients, %						
Aggravated asthma	6.2	8.1	7.1	7.8	14.8	12.6
Headache	5.0	8.5	10.8	9.3	6.6	7.8
Infection	2.5	2.3	3.7	2.9	7.0	2.9
Pharyngitis	13.3	16.2	13.3	13.7	13.6	9.7
Increased cough	1.8	3.1	2.4	2.3	3.3	4.9
Source: Tab 3 of the submission						

Adverse event data from the original NDA are described in Seetion IV of Dr. Anthracite's medical review. Increased infection was also seen among the elderly patients in the original NDA. In the original NDA, patients >55 years were defined as elderly, which deviates from the current regulatory definition of "elderly" as subjects ≥65 years [21 CFR 201.57 (f) (10)]. In the placebo-controlled studies infection was the only adverse event that occurred with an increased frequency in zafirlukast treated elderly patients. The frequency of infection was 13.3% (23/173) in the zafirlukast treated patients, and 2.9% (3/104) in the placebo treated patients. Infections reported were mostly the lower respiratory tract. Increased frequency of infection was not associated with any impressive changes in the total white blood cell count, neutrophil count, or lymphocyte count. Shift tables describing the data can be found in Dr. Anthracite's review.

Literature search was done using two terms, "Accolate and over-65", and "Accolate and elderly" (Ref: Tab 4 of the submission). The search covered the period between March 1995 and May 1999. A total of 63 documents were identified. Most of the articles did not reveal any new information. A review published by NC Barnes (Clinical tolerability of zafirlukast, a new oral antileukotriene drug, European Respiratory Review 1998; 8(54): 194-8) was of interest. This review summarized the safety of zafirlukast in 93 clinical trials involving 5,188 patients taking zafirlukast, and 2,573 patients taking placebo. For patients over 65 years (n=240), increased incidence of infection was reported (7.8% for zafirlukast vs 1.4% for placebo). The infections were mild and did not result in withdrawal from therapy. For patients 18 to 64 years (n=7,156), there was no increased infection with zafirlukast. For patients 12 to 18 years (n=346), there was a lower incidence of infection with zafirlukast (1.8% for zafirlukast vs 4.9% for placebo).

Spontaneous post-marketing adverse events were compiled and submitted (Tab 5). The date of the compilation is April 13, 1999. Six adverse events (bleeding/bruising, Churg Strauss, eosinophilia, liver events, myalgia/arthralgia, and vasculits) were categorized by age (12 to <18 years, 18 to 64 years, and >64 years). The adverse event "infection" was not included. Of the six adverse events, only eosinophilia was reported by a slightly greater percentage of patients >64 years (7.3%), than by other age groups (6.5% for 18 to 64 years, and 5.4% for 12 to 18 years).

Summary

The sponsor has submitted adequate information on the use of zafirlukast in the elderly patients (patients ≥65 years). The sponsor has demonstrated that zafirlukast at a dose of 20 mg by mouth twice a day can be safety given to the elderly patients. However, the risk-benefit ratio is less favorable for the elderly. In the ACCEPT trial, and in the sponsor's database, overall frequency of adverse events was noted to be higher in the elderly patients as compared to the adolescent and adult patients. Infections, particularly of the lower respiratory tract, were more frequently seen in the elderly patients in the sponsor's NDA studies. The large ACCEPT trial did not show increased incidence of infection in the elderly patients. Results of the ACCEPT trial suggest that the efficacy of zafirlukast is diminished in the elderly patients as compared to the adolescent and adult patients. In the pharmacokinetic

study, elderly patients had about two-fold higher Cmax and AUC as compared to the young adults. Taken together, these data suggest that zafirlukast can be safely given to patients ≥65 years of age, however, the risk-benefit ratio is less favorable in the elderly.

Specific labeling comments regarding the "Geriatric Use" subsection of the package insert will be forwarded separately to the sponsor. The "Geriatric Use" subsection of the package insert will be reflective of the database. The pharmacokinetic data described above will be retained as proposed by the sponsor. Safety and efficacy summary of the ACCEPT trial will be retained in the label. However, the language will be different than that proposed by the sponsor. Safety assessment from the sponsor's database that was used for the European Union submission will be retained. The language will again be different than that proposed by the sponsor. Any efficacy claim based on the European Union submission will be removed, since efficacy was not analyzed and submitted for our review. Reference to the

Recommended labeling for the "Geriatric Use" subsection

Based on cross study comparison, the clearance of zafirlukast is reduced in patients 65 year and older such that Cmax and AUC are approximately 2- to 3-fold greater than those of younger patients (see DOSAGE AND ADMINISTRATION, clinical pharmacology sections).

A total of 8094 patients were exposed to zafirlukast in North American and European short-term placebo-controlled clinical trials. Of these, 243 patients were elderly (≥65 years). No overall difference in adverse events was were seen in the elderly patients, except for an increase in the frequency of infection among zafirlukast treated elderly patients compared to placebo treated elderly patients (7.0% vs 2.9%). The infections were not severe, occurred mostly in the lower respiratory tract, and did not necessitate withdrawal of therapy.

An open-label, uncontrolled, 4-week trial of 3759 asthma patients compared the safety and efficacy of ACCOLATE 20 mg given twice daily in three patient age groups, adolescents (12-17 years), adults (18-65 years), and elderly (≥66 years).

In the elderly patients, adverse events occurring in greater than 1% of the population included headache (4.7%), diarrhea (1.8%), nausea (1.8%), and pharyngitis (1.3%). The elderly reported the lowest percentage of infections of all three age groups in this study.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-547/S011

CORRESPONDENCE

PROJECT MANAGER'S LABELING REVIEW

FEB - 7 2000

NDA: 20-547/S-011
Project Manager: Parinda Jani
PRODUCT: ACCOLATE (zafirlukast) Tablets 20 mg
SPONSOR: Zeneca Pharmaceuticals
SUBMISSION DATE: August 10, 1999
November 29, 1999

On August 10, 1999, Zeneca submitted supplement S-011, which provides for a revised package insert with changes to the Geriatric Use subsection of the PRECAUTIONS section. The changes approved in S-007 (approved September 17, 1999) are incorporated in the November 29, 1999, submission.

The labeling submitted November 29, 1999, was compared to the labeling approved for supplements S-007 and S-008. The medical officer has recommended the following changes to the PRECAUTIONS:Geriatric Use subsection.

"Based on cross study comparison, the clearance of zafirlukast is reduced in patients 65 year of age and older such that Cmax and AUC are approximately 2- to 3-fold greater than those of younger patients (see DOSAGE AND ADMINISTRATION, and CLINICAL PHARMACOLOGY sections).

A total of 8094 patients were exposed to zafirlukast in North American and European short-term placebo-controlled clinical trials. Of these, 243 patients were elderly (age 65 years and older). No overall difference in adverse events was seen in the elderly patients, except for an increase in the frequency of infection among zafirlukast treated elderly patients compared to placebo treated elderly patients (7.0% vs 2.9%). The infections were not severe; occurred mostly in the lower respiratory tract, and did not necessitate withdrawal of therapy.

An open-label, uncontrolled, 4-week trial of 3759 asthma patients compared the safety and efficacy of ACCOLATE 20 mg given twice daily in three patient age groups, adolescents (12-17 years), adults (18-65 years), and elderly (greater than 65 years). A higher percentage of elderly patients (n=384) reported — adverse events when compared to adults and adolescents. These elderly patients showed less improvement in the efficacy measures. In the elderly patients, adverse events occurring in greater than 1% of the population included headache (4.7%), diarrhea and nausea (1.8%), and pharyngitis (1.3%). The elderly reported the lowest percentage of infections of all three age groups in this study."

On February 7, 2000, in a teleconference, Mr. Mark DeSiato of Zeneca Pharmaceuticals agreed to the above recommended changes.

The remainder sections are unchanged.

Recommendation: Supplement S-011 should be approved with the changes listed above. A draft approval letter is attached.

/S/

Parinda Jani
Project Manager

CC:
ORIG NDA 20-547
DIV FILE/HFD-570
HFD-570/JANI/
HFD-570/ANTHRACITE /S/ 2/7/2000
HFD-570/CHOWDHURY

APPEARS THIS WAY
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BL
SLR-011
NDA SUPPLEMENT

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ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.

1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

SENT VIA UPS NEXT DAY AIR

NOV 29 1999

Robert Meyer, MD
Division Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 570, Room No. 10B-03
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Meyer:

Re: ACCOLATE® (zafirlukast) Tablets
NDA 20-547/S-011
Response to FDA Request for Information - Labeling

Reference is made to a telephone conversation of October 28, 1999 between Ms. Parinda Jani of the Division of Pulmonary Drug Products and Mr. Mark DeSiato of Zeneca Pharmaceuticals.

During this conversation, Ms. Jani requested that Zeneca provide in an electronic format the draft labeling submitted by Zeneca in the above referenced supplemental New Drug Application (sNDA) on August 11, 1999.

Accordingly, attached hereto in Tab A are two diskettes which contain an electronic version of the draft labeling in Word 7.0 format. This labeling incorporates the current version of the ACCOLATE® (zafirlukast) Tablets (Rev J 09/99) professional information, and the identical labeling revisions contained in the draft labeling submitted to the above referenced sNDA on August 11, 1999.

Provided in Tab B is an 8½ x 11 hard copy of the labeling contained in each diskette. The revisions are underlined for ease of review. In addition, provided in Tab C is a three column document; the left column contains the current labeling for ACCOLATE (Rev J 09/99); the middle column contains the proposed revisions; and in the right column comments, where appropriate.

The diskettes provided have been scanned by the Norton Anti-Virus Program (version 5.00.00, Virus Definition date 10/14/99), and the results are included.

Please contact me if you have any questions or require information.

Sincerely,

Mark A. DeSiato

Mark A. DeSiato
Director, Respiratory
Regulatory Affairs Department
(302) 886-8510
(302) 886-2822 (fax)

MAD/TGU/jr
Enclosures

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