CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-547/S011

APPROVAL LETTER
NDA 20-547/S-011

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
AC1205 Raw N 09/00

PROFESSIONAL INFORMATION BROCURE

ACCOLATE
ZAFIRUKAST

DESCRIPTION
Zafirlukast is a synthetic, selective leukotriene antagonists receptor antagonist (LETRA), with the chemical name 6-(2-chlorophenyl)-1-methyl-8-(2,3-dihydro-4H-pyrido[1,2-a]pyrimidin-7-yl)oxy-2,5-norbornadiene. The molecular weight of zafirlukast is 287.3 and the structural formula is...

The empirical formula is C_{21}H_{24}ClNO_{2}

Zafirlukast, a white, amorphous powder, is leucocyte and mast cell degranulation products and platelet aggregation. AC Collate is supplied as 10 mg and 20 mg tablets for oral administration.

Active ingredients: Film-coated tablets containing crystalline zafirlukast, lactose, magnesium stearate, cellulose, colloidal silicon dioxide, talc. Tablets contain 10 mg or 20 mg of zafirlukast, respectively.

CLINICAL PHARMACOLOGY
Mechanism of Action: Zafirlukast is a selective and competitive antagonist of leukotrienes D_{4} and E_{4} (LT D_{4} and LT E_{4}) receptors. These leukotrienes are synthesized in the body to regulate inflammatory processes.

Clinical Pharmacokinetics: Absorption: Absorption of zafirlukast is rapid and complete after oral administration. The mean bioavailability of zafirlukast tablets is about 50%.

Distribution: Zafirlukast is more than 99% bound to plasma proteins, predominantly albumin. The degree of binding was similar in patients with renal impairment.

Metabolism: Zafirlukast is highly metabolized in the liver. The primary metabolites are conjugates of zafirlukast with glucuronic acid and sulfate, and these metabolites are excreted in urine.

Elimination: The elimination phase is characterized by a tri-exponential decay, with a terminal phase half-life of approximately 10 hours.

ACCOLATE (zafirlukast) Tablets

In a second and smaller study, the effect of ACOLATE on mean end-expiratory volume was comparable to the active comparator. For function, there was no significant difference on the primary endpoint of time to bronchodilator use (figure below).

Mean (95% CI) - bronchodilator use (puff/day)

In these trials, improvement in asthma symptoms occurred within one week of initiating treatment with ACOLATE. The onset of clinical action is 24 hours after starting treatment. Patients receiving asthma therapy other than oral corticosteroids should be carefully monitored when oral corticosteroids are initiated or withdrawn during ACOLATE therapy. The use of ACOLATE is not recommended in patients with gastroesophageal reflux disease.

INDICATIONS AND USAGE
ACOLATE is indicated for the prophylaxis and treatment of asthma in adults and children 7 years of age and older.

CONTRAINDICATIONS
ACOLATE is contraindicated in patients who are hypersensitive to zafirlukast or any of the inactive ingredients.

WARNINGS
ACOLATE is indicated for use in the reversal of bronchospasm in acute asthma exacerbations in patients with asthma responsive to inhaled short-acting beta-agonists. Therapy with ACOLATE can be continued for the prevention of asthma exacerbations.

ACOLATE should be used with caution in patients requiring long-term corticosteroid therapy for asthma.

PRECAUTIONS
Patients with asthma receiving ACOLATE should be monitored closely and adenosine dose adjusted accordingly to ensure that there is no bronchodilator. The risk of adverse effects of ACOLATE may be increased when used with other bronchodilators.

Patients should be instructed to take ACOLATE at least 1 hour before or 2 hours after meals.

When ACOLATE is administered, the risk of adverse effects should be monitored. The inhalation of particles may result in bronchoconstriction.

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Patients with asthma receiving ACOLATE should be monitored closely and adenosine dose adjusted accordingly. The risk of adverse effects of ACOLATE may be increased when used with other bronchodilators.

Patients should be instructed to take ACOLATE at least 1 hour before or 2 hours after meals.

When ACOLATE is administered, the risk of adverse effects should be monitored. The inhalation of particles may result in bronchoconstriction.
ACCOLATED (zafirlukast) Tablets

The effectiveness of ACCOLATE for the prophylaxis and chronic treatment of attacks in pediatric patients aged 7 to 11 years with aspirin-induced asthma has been demonstrated by ACOLLATET in adults with asthma, and the same course of pharmacology and the dose effects are substantially similar in children (see CLINICAL PHARMACOLOGY and PRECAUTIONS - Drug Interaction section).

Rapid cases of patients experiencing increased aspirin tolerance or with aspirin clinical signs or symptoms of intolerance may be observed in patients treated with ACOLLATET. Additional aspirin therapy should be administered cautiously and only under the guidance of hematologist or other appropriate medical personnel.

Pediatric Patients 0 to 11 Years of Age

ACCOLATE has not been studied in pediatric patients. The safety and efficacy of ACOLLATET in pediatric patients aged 7 to 11 years with aspirin-induced asthma have been demonstrated by ACOLLATET in adults with asthma, and the same course of pharmacology and the dose effects are substantially similar in children (see CLINICAL PHARMACOLOGY and PRECAUTIONS - Drug Interaction section).

ADVERSE EFFECTS

Adolescents and Children 12 years of age and older

The safety database for ACOLLATET includes more than 4,000 healthy volunteers and patients who received ACOLLATET, of whom approximately 50% were adults and 50% children. The most common adverse events reported were headache, nausea, and diarrhea. The incidence of these events occurring greater that 1% in the placebo-controlled trials was headache (0.7%), nausea (0.5%), and vomiting (0.3%). The incidence of these events occurring greater that 1% in the safety study of the pediatric patients with aspirin-induced asthma was headache (8.8%), nausea (3.8%), and vomiting (1.6%).

Clinical studies of ACOLLATET in children aged 12 years of age and older who were treated with ACOLLATET are ongoing.

This section contains a summary of the dosage adjustment of ACOLLATET in pediatric patients based on a single-dose trial in children aged 6 to 11 years and a double-blind, placebo-controlled trial in children aged 12 years of age and older.

ACCOLATE 10 mg Tablets, NDC 0101-0001-01 white, uncoated, round tablets labeled "ZENATRA" are supplied in packages of 60 tablets and hospital Use Dose (NDC 0101-0009-01 white, uncoated, round tablets labeled "ZENA" are supplied in packages of 60 tablets and hospital Use Dose (NDC 0101-0010-01 white, uncoated, round tablets labeled "ZENATA" are supplied in packages of 60 tablets and hospital Use Dose (NDC 0101-0011-01 white, uncoated, round tablets labeled "ZENATAC" are supplied in packages of 60 tablets and hospital Use Dose (NDC 0101-0012-01 white, uncoated, round tablets labeled "ZENATAC" are supplied in packages of 60 tablets and hospital Use Dose (NDC 0101-0013-01 white, uncoated, round tablets labeled "ZENATAC" are supplied in packages of 60 tablets and hospital Use Dose (NDC 0101-0014-01 white, uncoated, round tablets labeled "ZENATAC" are supplied in packages of 60 tablets and hospital Use Dose (NDC 0101-0015-01 white, uncoated, round tablets labeled "ZENATAC" are supplied in packages of 60 tablets and hospital Use Dose (NDC 0101-0016-01 white, uncoated, round tablets labeled "ZENATAC" are supplied in packages of 60 tablets and hospital Use Dose (NDC 0101-0017-01 white, uncoated, round tablets labeled "ZENATAC" are supplied in packages of 60 tablets and hospital Use Dose (NDC 0101-0018-01 white, uncoated, round tablets labeled "ZENATAC" are supplied in packages of 60 tablets and hospital Use Dose (NDC 0101-0019-01 white, uncoated, round tablets labeled "ZENATAC" are supplied in packages of 60 tablets and hospital Use Dose (NDC 0101-0020-01 white, uncoated, round tablets labeled "ZENATAC" are supplied in packages of 60 tablets and hospital Use Dose (NDC 0101-0021-01 white, uncoated, round tablets labeled "ZENATAC" are supplied in packages of 60 tablets and hospital Use Dose (NDC 0101-0022-01 white, uncoated, round tablets labeled "ZENATAC" are supplied in packages of 60 tablets and hospital Use Dose (NDC 0101-0023-01 white, uncoated, round tablets labeled "ZENATAC" are supplied in packages of 60 tablets and hospital Use Dose (NDC 0101-0024-01 white, uncoated, round tablets labeled "ZENATAC" are supplied in packages of 60 tablets and hospital Use Dose (NDC 0101-0025-01 white, uncoated, round tablets labeled "ZENATAC" are supplied in packages of 60 tables...
Draft Labeling
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

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RELATED APPLICATIONS (if applicable)

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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 Zenna 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
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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 FEV₁₀'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).
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 FEV₁₀ 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 FEV₁₀'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., FEV1.0. 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 FEV1.0'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 FEV₁,₀) obtained by ———— device
- had a completed CRF including one week of asthma scores

The safety data base consisted of all enrolled patients [Tab 1:8, 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 1:8]. 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 FEV₁,₀; 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].

<table>
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<td>&gt; 20</td>
<td>0 (0)</td>
<td>960 (37)</td>
<td>131 (41)</td>
<td></td>
</tr>
<tr>
<td>NR*</td>
<td>2 (&lt;1)</td>
<td>10 (&lt;1)</td>
<td>2 (&lt;1)</td>
<td></td>
</tr>
<tr>
<td>ASTHMA SEVERITY</td>
<td>mild</td>
<td>40 (15)</td>
<td>233 (11)</td>
<td>27 (8)</td>
</tr>
<tr>
<td>severe</td>
<td>42 (16)</td>
<td>507 (19)</td>
<td>94 (29)</td>
<td></td>
</tr>
<tr>
<td>NR*</td>
<td>3 (1)</td>
<td>57 (2)</td>
<td>4 (1)</td>
<td></td>
</tr>
<tr>
<td>MEAN FEV 1,0 (% pred)</td>
<td>75.5</td>
<td>74.2</td>
<td>73.3</td>
<td></td>
</tr>
<tr>
<td>ER visit in last year</td>
<td>77 (29)</td>
<td>680 (26)</td>
<td>53 (17)</td>
<td></td>
</tr>
<tr>
<td>Hospitalized in last year</td>
<td>39 (15)</td>
<td>308 (12)</td>
<td>38 (12)</td>
<td></td>
</tr>
<tr>
<td>PREVIOUS TREATMENT</td>
<td>SAB2*</td>
<td>56 (21)</td>
<td>486 (19)</td>
<td>44 (14)</td>
</tr>
<tr>
<td>NS*+SAB2</td>
<td>37 (14)</td>
<td>295 (11)</td>
<td>39 (12)</td>
<td></td>
</tr>
<tr>
<td>ICS*+SAB2</td>
<td>70 (27)</td>
<td>624 (24)</td>
<td>76 (24)</td>
<td></td>
</tr>
<tr>
<td>SAB2+NS+ICS</td>
<td>100 (38)</td>
<td>1137 (46)</td>
<td>162 (50)</td>
<td></td>
</tr>
</tbody>
</table>

*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].

<table>
<thead>
<tr>
<th>Measure</th>
<th>n</th>
<th>Adolescents</th>
<th>n</th>
<th>Adults</th>
<th>n</th>
<th>Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM PEFR (L/min)</td>
<td>218</td>
<td>2520</td>
<td>263</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (SD)</td>
<td></td>
<td>353.1 (100.8)</td>
<td></td>
<td>357.5 (112.5)</td>
<td></td>
<td>265.1 (111.3)</td>
</tr>
<tr>
<td>LS change (SE)</td>
<td></td>
<td>45.3 (5.9)</td>
<td></td>
<td>35.8 (1.8)</td>
<td></td>
<td>14.6 (5.5)</td>
</tr>
<tr>
<td>PM PEFR (L/min)</td>
<td>234</td>
<td>2285</td>
<td>264</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (SD)</td>
<td></td>
<td>379.7 (93.8)</td>
<td></td>
<td>375.9 (112.8)</td>
<td></td>
<td>280.8 (105.6)</td>
</tr>
<tr>
<td>LS change (SE)</td>
<td></td>
<td>41.0 (5.9)</td>
<td></td>
<td>31.4 (1.9)</td>
<td></td>
<td>10.8 (5.7)</td>
</tr>
<tr>
<td>AM FEV 1.0 (L)</td>
<td>218</td>
<td>2250</td>
<td>263</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (SD)</td>
<td></td>
<td>2.59 (0.87)</td>
<td></td>
<td>2.34 (0.89)</td>
<td></td>
<td>1.55 (0.65)</td>
</tr>
<tr>
<td>LS change (SE)</td>
<td></td>
<td>0.35 (0.06)</td>
<td></td>
<td>0.22 (0.02)</td>
<td></td>
<td>0.07 (0.05)</td>
</tr>
<tr>
<td>PM FEV 1.0 (L)</td>
<td>234</td>
<td>2285</td>
<td>264</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (SD)</td>
<td></td>
<td>2.72 (0.86)</td>
<td></td>
<td>2.41 (0.86)</td>
<td></td>
<td>1.62 (0.64)</td>
</tr>
<tr>
<td>LS change (SE)</td>
<td></td>
<td>0.39 (0.05)</td>
<td></td>
<td>0.21 (0.02)</td>
<td></td>
<td>0.06 (0.05)</td>
</tr>
</tbody>
</table>

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.
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 respondents 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.
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].

Although compliance was said to have been monitored, I could find no mention of it in the draft report nor in the journal article.
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 ISSN 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 ISSN 109:262-6].

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; Date Review; Accolate; 4-Month UPDT; Analysis/Reporting; Data Set = ADVERSE; Analysis Program = AE's by Dose - Placebo, (AE's) By Exposure - P-acebo, AE's by (duration of treatment) and Trial Group; Selection Variable = Age Entry (grouped); Selection Value > 55].
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 [CANAD; Data Review; 4-Month UPDT; Analysis/Reporting; Data Set = ADVERSE; Analysis Program = AE's in Patients - Placebo; with Saved Subsets: Age Entry (grouped) > 55; Race = Caucasian, Black, Other; or, Sex = Male or Female].
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 database.

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_LYMPS; Analysis Program = Mean Labs BEF/END TRT; ± Saved Subsets: Selection Variable = Age Entry (grouped) <18, 18-55, >55].

### Table: Baseline and End-of-Treatment Change in White Blood Cell Count, Neutrophils and Lymphocytes for Each Treatment Group, Over 55 Years of Age

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Zafirlukast: mean (S.D.)</th>
<th>Placebo: mean (S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n Before Treatment</td>
<td>Change - End of Treatment</td>
</tr>
<tr>
<td>WBC (x10^9/L)</td>
<td>308 6.64 (1.63)</td>
<td>0.01 (1.45)</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>199 59.55 (9.39)</td>
<td>-1.31 (8.91)</td>
</tr>
<tr>
<td>Lymphs (%)</td>
<td>200 29.31 (8.40)</td>
<td>0.61 (7.21)</td>
</tr>
</tbody>
</table>

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_LYMPS; 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 = AVERSEV; 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].

<table>
<thead>
<tr>
<th>PATIENTS REPORTING AE = &quot;Infection&quot; DURING OPEN-LABEL TRIALS</th>
<th>(4-Month Safety Update, open-label trials) [CANDA Table T3.2.4.3]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category</td>
<td>At Risk</td>
</tr>
<tr>
<td>----------</td>
<td>---------</td>
</tr>
<tr>
<td>AGE</td>
<td></td>
</tr>
<tr>
<td>≤ 55 years</td>
<td>816</td>
</tr>
<tr>
<td>&gt; 55 years</td>
<td>130</td>
</tr>
<tr>
<td>SEX (Age &gt; 55)</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>65</td>
</tr>
<tr>
<td>Females</td>
<td>65</td>
</tr>
<tr>
<td>TOTAL (all ages)</td>
<td>946</td>
</tr>
</tbody>
</table>

All patients > 55 years of age who reported infections were Caucasian, a racial group that represented 90.4% of all patients in this database. 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)].


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 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/arthritis
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  | Total Patients  | % Of Age Group  |
|                 |                 | With AE         | In Age Group    |                 |
| Eosinophilia    | 12 to ≤18       | 4               | 74              | 5.4             |
|                 | 18 to 64        | 56              | 884             | 8.5             |
|                 | 84+             | 24              | 328             | 7.3             |
|                 | Unknown         | 8               | 365             | 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, Zeneca’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 Pharmacoepidemiology 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 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. Domiciliary-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 FEV1 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*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Adolescents (n = 218 to 234)</th>
<th>Age Group</th>
<th>Elderly (n = 263 to 291)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning FEV1 (L)</td>
<td>2.59 → 0.35</td>
<td>2.34 → 0.22</td>
<td>1.55 → 0.07</td>
</tr>
<tr>
<td>Evening FEV1 (L)</td>
<td>2.72 → 0.39</td>
<td>2.41 → 0.21</td>
<td>1.62 → 0.06</td>
</tr>
<tr>
<td>Morning PEFR (L/min)</td>
<td>353.1 → 45.3</td>
<td>357.5 → 35.8</td>
<td>265.1 → 14.6</td>
</tr>
<tr>
<td>Evening PEFR (L/min)</td>
<td>379.7 → 41.0</td>
<td>375.9 → 31.4</td>
<td>280.8 → 10.8</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Measure</th>
<th>Adolescents (n = 218 to 234)</th>
<th>Adults (n = 2250 to 2285)</th>
<th>Elderly (n = 263 to 291)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma symptom score</td>
<td>7.86 → 3.12</td>
<td>8.88 → 2.67</td>
<td>9.35 → 2.18</td>
</tr>
<tr>
<td>Beta-agonist use (puffs/day)</td>
<td>4.49 → -1.72</td>
<td>6.12 → -1.52</td>
<td>6.21 → -0.59</td>
</tr>
<tr>
<td>Nighttime awakening (#/wk)</td>
<td>1.37 → -0.85</td>
<td>2.03 → 0.94</td>
<td>1.61 → -0.74</td>
</tr>
<tr>
<td>Morning with asthma (#/wk)</td>
<td>2.97 → -1.94</td>
<td>4.02 → 1.50</td>
<td>3.45 → -1.32</td>
</tr>
</tbody>
</table>

* 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

<table>
<thead>
<tr>
<th>Type of adverse event, %</th>
<th>Adolescents (n = 312)</th>
<th>Adults (n = 3021)</th>
<th>Elderly (n = 384)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>11.5</td>
<td>17.5</td>
<td>18.8</td>
</tr>
<tr>
<td>Treatment related AE</td>
<td>4.2</td>
<td>7.4</td>
<td>8.1</td>
</tr>
<tr>
<td>Serious AE</td>
<td>1.6</td>
<td>0.9</td>
<td>2.3</td>
</tr>
<tr>
<td>Treatment related SAE</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Adverse events occurring in ≥1% of patients, n (%)

| Headache (3.5) | 11             | 109 (3.6)        | 18 (4.7)          |
| Infection (1.3) | 4 (0.6)        | 19 (0.6)         | 1 (0.3)           |
| Abdominal pain (0.0) | 8 (0.3)        | 4 (1.0)          |
| Diarrhea (1.0) | 3 (0.8)        | 24 (1.5)         | 7 (1.8)           |
| Nausea (0.6) | 2 (1.5)        | 45 (1.5)         | 7 (1.8)           |
| Pharyngitis (1.3) | 4 (1.4)        | 5 (1.3)          |
| Sinusitis (1.0) | 3 (1.3)        | 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 PHARMACOLOGY - "Clinical Pharmacokinetics and Bioavailability" section (Tab 3 of the submission).
Table 3. Demographics of subjects exposed to zafirlukast in North American and European trials*

<table>
<thead>
<tr>
<th></th>
<th>Short-Term Trials</th>
<th></th>
<th>Long-Term Trials (at 20 mg BID)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zafirlukast</td>
<td>Placebo</td>
<td>Zafirlukast</td>
</tr>
<tr>
<td>Number of trials</td>
<td>107</td>
<td>75</td>
<td>8</td>
</tr>
<tr>
<td>Subjects exposed</td>
<td>8094</td>
<td>3922</td>
<td>1242</td>
</tr>
<tr>
<td>Age, mean (range)</td>
<td>34.9 (5-79)</td>
<td>34.7 (5-77)</td>
<td>37.9 (12-76)</td>
</tr>
<tr>
<td>Age distribution, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 to 11 years</td>
<td>270 (3.3)</td>
<td>130 (3.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>12 to &lt;18 years</td>
<td>564 (7.0)</td>
<td>260 (6.6)</td>
<td>98 (7.9)</td>
</tr>
<tr>
<td>18 to 64 years</td>
<td>7017 (86.7)</td>
<td>3429 (87.4)</td>
<td>1099 (88.5)</td>
</tr>
<tr>
<td>&gt;65 years</td>
<td>243 (3.0)</td>
<td>103 (2.6)</td>
<td>45 (3.6)</td>
</tr>
</tbody>
</table>

* 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

<table>
<thead>
<tr>
<th></th>
<th>Age Groups</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12-17 years</td>
<td>18-64 years</td>
<td>&gt;65 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zafirlukast (n = 564)</td>
<td>Placebo (n = 260)</td>
<td>Zafirlukast (n = 7017)</td>
<td>Placebo (n = 3429)</td>
<td>Zafirlukast (n = 243)</td>
<td>Placebo (n = 103)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of adverse event, %</th>
<th>12-17 years</th>
<th>18-64 years</th>
<th>&gt;65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>37.8</td>
<td>47.7</td>
<td>48.7</td>
</tr>
<tr>
<td>AE with withdrawal</td>
<td>1.1</td>
<td>1.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Serious AE</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>SAE with withdrawal</td>
<td>0.7</td>
<td>0.4</td>
<td>0.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse events occurring ≥3% of patients, %</th>
<th>12-17 years</th>
<th>18-64 years</th>
<th>&gt;65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggravated asthma</td>
<td>6.2</td>
<td>8.1</td>
<td>7.1</td>
</tr>
<tr>
<td>Headache</td>
<td>5.0</td>
<td>8.5</td>
<td>10.8</td>
</tr>
<tr>
<td>Infection</td>
<td>2.5</td>
<td>2.3</td>
<td>3.7</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>13.3</td>
<td>16.2</td>
<td>13.3</td>
</tr>
<tr>
<td>Increased cough</td>
<td>1.8</td>
<td>3.1</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Source: Tab 3 of the submission

Adverse event data from the original NDA are described in Section 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/arthritis, and vasculitis) 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 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.
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 ON ORIGINAL
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 DeSiatto 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
Director, Respiratory
Regulatory Affairs Department
(302) 886-8510
(302) 886-2822 (fax)

MAD/TGU/jr
Enclosures

Desk Copies: Ms. Parinda Jani, HFD 570, Room No. 10B-45 (Cover Letter Only)
Dr. Raymond Anthracite, HFD 570, Room No. 10B-45 (Cover Letter Only)