DEPARTMENT OF HEALTH & HUMAN SERVICES COPY Public Health Service

96/201

NDA 20-547

Food and Drug Administration
Rockville MD 20857

INDEX 133

SEP 26 1996

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

Attention: Donna M. Dea
Senior Regulatory Specialist, Drug Registration
Drug Regulatory Affairs Department

Dear Ms. Dea:

Please refer to your pending new drug application dated June 26, 1995, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Accolate (zafirlukast) 20 mg Tablets.

We acknowledge receipt of your amendments dated June 26, July 7 and 10, August 2 and 4, October 25, November 7, 20, 22, and 30, and December 5, 20, and 21, 1995, and February 2, 7, 8, 12, 14, 15, 20, and 22, March 4, 6, 8, 15, 21, and 27, April 5, 23, 26, and 30, May 2, 3, 7, 10, 17, 21, and 22, June 17, 18, 19, and 24, July 12, 22, and 24, August 2, 9, 14, 15, and 22, and September 3, 5, 6, and 25, 1996. Your submission dated March 27, 1996, extended the user fee due date to September 26, 1996.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for the prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older as recommended in the draft physician labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft physician labeling submitted on September 25, 1996, and the September 6, 1996, mock-up carton and container labels. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

RECEIVED
OCT 1 1996
DRUG REGULATORY AFFAIRS

Please submit 16 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 NDA 20-547." Approval of this submission by FDA is not required before the FPL may be used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of the labeling may be required.

We remind you of your Phase 4 commitments specified in your submissions dated March 27, May 21, June 17 and 19, July 24, August 21, and September 3, 1996. These commitments are listed below.

1. As more experience is gained with the commercial-scale batches of Accolate, the limit for anhydrous crystalline content of the drug substance will be reviewed with the intent of reducing the limit, if appropriate. Progress will be reported in your annual reports to this NDA.

2. When techniques become available and are shown to be capable of measuring the crystalline monohydrate level in amorphous zafirlukast below the current limit of quantification of 1.5% w/w, a new method will be adopted. Progress will be reported in your annual reports to this NDA.

3. Once a new method has been developed, an Action Limit of 6%, in the presence of a release specification limit of 10% crystalline monohydrate, will be established for the drug product.

4. Reference spectra of packaging components will be submitted by October 31, 1996.

5. A method for the determination of the anhydrous crystalline form of the drug substance in the tablet will be developed and validated by November 1, 1996.

6. Appropriate studies will be conducted with test results at times 0 and 6 months for the effect of excipients on the conversion of the amorphous form to the anhydrous crystalline form that will be reported by February 15, 1997.

7. Further studies will be conducted to investigate the epigenetic mechanism for the development of urinary bladder transitional cell papillomas in rats.

Protocols, data, and final reports related to the Phase 4 commitments should be submitted to this NDA as correspondence. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated as "Phase 4 Commitments."

As agreed, a tentative quantification limit of 25% of anhydrous crystalline form of the drug substance in tablets and an action (detection) limit of 15% will be established immediately, and stability data for the first 3 commercial batches of Accolate tablets after 6-month storage will be reported by February 15, 1997.

Also as agreed, should the test during stage 2/3 of the synthesis need to be omitted after approval, a supplement requiring pre-approval with supporting data will be submitted.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any deficiencies that may occur.

Please submit one market package of the drug product when it is available.

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, please contact:

Parinda Jani
Project Manager
(301) 827-1057

Sincerely yours,

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

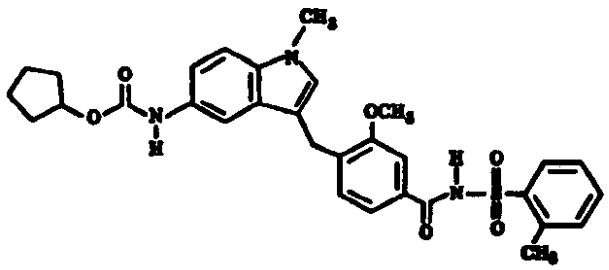
SIC XXXXX-XX
PCC XXXXX-XX

PROFESSIONAL INFORMATION BROCHURE

ACCOLATE® Tablets
(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-tolylsulfonylbenzamide. The molecular weight of zafirlukast is 575.7 and the structural formula is:



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

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

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

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

CLINICAL PHARMACOLOGY

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

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

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

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

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

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

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

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

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

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

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

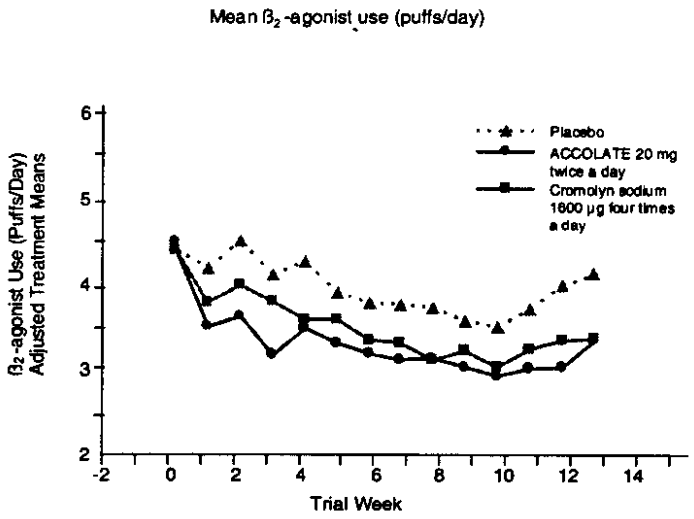
Clinical Studies: Three U.S. double-blind, randomized, placebo-controlled, 13-week clinical trials in 1,380 patients with mild-to-moderate asthma demonstrated that ACCOLATE improved daytime asthma symptoms, nighttime awakenings, mornings with asthma symptoms, rescue $beta_2$-agonist use, FEV_1, and morning peak expiratory flow rate. In these studies, the patients had a mean baseline FEV_1 of approximately 75% of predicted normal and a mean baseline beta-agonist requirement of approximately 4-5 puffs of albuterol per day. The results of the largest of the trials are shown in the table below.

Table 1. Mean Change from Baseline at Study Endpoint

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

*$p<0.05$, compared to placebo

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



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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

WARNINGS

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

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.

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

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

Co-administration of zafirlukast (80 mg/day) at steady state with a single dose of a liquid theophylline preparation (6 mg/kg) in 13 asthmatic patients resulted in decreased mean plasma levels of zafirlukast by approximately 30%, but no effect on plasma theophylline levels was observed.

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

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

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

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

Reproduction and fertility studies in rats showed no effect on fertility due to zafirlukast at doses up to 2000 mg/kg (approximately 400 times the maximum recommended human daily oral dose on mg/m^2 basis). In the one-year toxicity studies in dogs, zafirlukast produced an increase in absolute and relative uterine and ovarian weights at an oral dose of 150 mg/kg, resulting in approximately 85 times the systemic exposure ($AUC_{0\text{-}12h}$) in humans at the maximum recommended human oral daily dose.

Pregnancy Category B: No teratogenicity was observed at oral doses up to 1600 mg/kg/day in mice (approximately 160 times the maximum recommended human daily oral dose on a mg/m^2 basis), 2000 mg/kg/day in rats (approximately 400 times the maximum recommended human daily oral dose on a mg/m^2 basis) and 2000 mg/kg/day in cynomolgus monkeys (approximately 800 times the maximum recommended human daily oral dose on a mg/m^2 basis). At 2000 mg/kg/day in rats, maternal toxicity and deaths were seen with increased incidence of early fetal resorption. Spontaneous abortions occurred in cynomolgus monkeys at a maternally toxic dose of 2000 mg/kg/day orally. There are no adequate and well-controlled trials in pregnant women. Because animal reproduction studies are not always predictive of human response, ACCOLATE should be used during pregnancy only if clearly needed.

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

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

ADVERSE REACTIONS

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

A comparison of adverse events reported by $\geq$ 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.

Although the frequency of hepatic transaminase elevations was comparable between zafirlukast and placebo-treated patients, a single case of symptomatic hepatitis and hyperbilirubinemia, without other attributable cause, occurred in a patient who had received 40 mg/day of zafirlukast for 100 days. In this patient, the liver enzymes returned to normal within 3 months of stopping ACCOLATE.

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

OVERDOSAGE

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

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

DOSAGE AND ADMINISTRATION

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

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

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

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

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

HOW SUPPLIED

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

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

Manufactured For:
Zeneca Pharmaceuticals
A Business Unit of Zeneca Inc.
Wilmington, DE 19850-5437

by:
IPR Pharmaceuticals Inc.

Rev A 09/96
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SIC XXXXX-XX
PCC XXXXX-XX

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II

DIVISION OF PULMONARY DRUG PRODUCTS

CDER Pulmonary Group (HFD-155), 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 827-1050 FAX: (301) 827-1271

TO: Donna Dea

FROM: Paunda Jain

Total number of pages, including cover sheet: 4

Date: 9.26.96

COMMENTS:

Approval letter for NDA - 20-547

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INCOMING OFFICIAL CORRESPONDENCE

FAXED FROM FDA

COPY 4

THE ATTACHED WAS RECEIVED FROM THE FDA IN LIEU OF OFFICIAL LETTERHEAD CORRESPONDENCE.

TO: Donna Dea

DRUG NAME: Accolate

IND OR (NDA) NUMBER: 20-547

DATE OF CORRESPONDENCE: September 26, 1996

DATE RECEIVED: September 27, 1996

DRAD. FOLDER
S. Acquaviva
S. Robinson
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