DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

**TRANSMITTED VIA FACSIMILE**

MAY 26 2000

Ms. Christine (Duffy) Smith
Leader, Promotional Regulatory Affairs
AstraZeneca L.P.
690 Lee Road (Building C)
Chesterbrook, PA 19087-5627

**RE: NDA# 20-547**
Accolate (zafirkulast) Tablets
MACMIS ID#: 9019

Dear Ms. Smith:

This letter concerns a piece of professional promotional labeling (i.e., visual aid AC1184) for Accolate (zafirkulast) Tablets disseminated by AstraZeneca Pharmaceuticals' (AstraZeneca). The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed this item and concluded that AstraZeneca is disseminating promotional labeling that lacks fair balance and is misleading. This promotional labeling violates the Federal Food, Drug, and Cosmetic Act and implementing regulations and should be discontinued immediately.

This 16-page visual aid promotes Accolate for children ages 7 to 11 years and to older children and adults. The piece includes several whole-page presentations promoting the safety of Accolate in adults (e.g., page 12 "The safety of Accolate in clinical studies", page 13 "The real-world safety of Accolate"). In each of these promotional safety discussions and in other presentations promoting the efficacy of Accolate, none of the accompanying fair balance disclosures includes PRECAUTION/ADVERSE EVENT information from the approved product labeling about Eosinophilic Conditions reported post-marketing. For such extended safety-related claims or other risk discussions, the systemic eosinophilia disclosure is important information to provide health professionals for a complete presentation of potential risks associated with use of this drug. Therefore, this visual aid is misleading because it lacks fair balance disclosure about systemic eosinophilia.

AstraZeneca should immediately cease its dissemination and use of all professional promotional materials containing such presentations for Accolate that lack the systemic eosinophilia risk disclosure. We should receive your written response no later than June 12, 2000, and it should list all similarly violative materials, with a description of your method of discontinuation.

Your response should be directed to the undersigned at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm 17-B-20, 5600 Fishers Lane, Rockville, MD 20857. We remind AstraZeneca that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID# 9019 in addition to the NDA number.

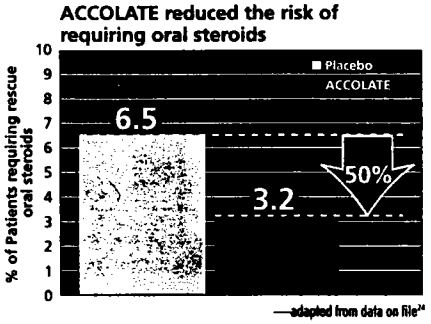
Sincerely,

/S/

Joan Hankin, JD
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

# The safety of ACCOLATE in clinical studies

ACCOLATE tablets reduced the risk of requiring oral steroids for asthma exacerbations by approximately 50% across five 13-week, placebo-controlled, double-blind trials[24]




—adapted from data on file[24]

## ACCOLATE was generally well tolerated in clinical trials[9]

| Adverse events (>3.0%) occurring more commonly in patients treated with ACCOLATE | ACCOLATE (N=4,058) | Placebo (N=2,032) | Statistical Significance |
|---|---|---|---|
| headache | 12.9% | 11.7% | NS |
| infection* | 3.5% | 3.4% | NS |
| nausea | 3.1% | 2.0% | NS |

NS=not significant.

*In clinical trials, an increased proportion of patients taking ACCOLATE over the age of 55 years reported infections as compared to placebo-treated patients. Infections were generally mild to moderate and predominantly of the respiratory tract.

- Routine liver function monitoring is not required at the recommended dose of 20 mg bid
  - —Rare elevations of one or more liver enzymes have been observed in clinical trials with ACCOLATE, mostly at four times the recommended dose[9]
  - —If clinical signs or symptoms of liver dysfunction are noted, it is reasonable to recommend standard liver tests be performed and the patient managed accordingly[9]
- To date, cataracts, glaucoma, osteoporosis, and ventricular arrhythmias have not been associated with the use of ACCOLATE
- In a clinical trial, ACCOLATE at 80 mg/day had no effect on plasma theophylline levels[9]

ACCOLATE®
ZAFIRLUKAST 20 mg Tablets

## OUR PROOF IS IN THE PEOPLE

Please see accompanying full prescribing information.

Dr. HELEN G.

IRENE S.

Wants to put safety first.

**IRENE S.**

Wants to put safety first.

# The real-world safety of ACCOLATE

## To date, over 1,000,000 patients have been treated[2] and over 3 million prescriptions written[3]

**In a 39-week, open-label extension (OLE), the safety profile of ACCOLATE was similar to that of the initial 13-week, double-blind trial[4,10]**

- Most common adverse events were pharyngitis and headache
- Rare cases of increased theophylline levels after the addition of ACCOLATE to an existing theophylline regimen have been reported[9]
  - —The mechanism of interaction in these patients is unknown, but physicians should exercise prudence when coadministering ACCOLATE and theophylline[9]

Patients should not modify any of their antiasthma medications unless instructed by a doctor.

Patients on oral warfarin anticoagulant therapy and ACCOLATE should have their prothrombin times monitored and anticoagulant dose adjusted accordingly.

Patients should notify their doctor if their medical condition worsens.

ACCOLATE®
ZAFIRLUKAST 20 mg Tablets

**OUR PROOF IS IN THE PEOPLE**

Please see accompanying full prescribing information.

## Dr. HELEN G.

Confident she can practice what she preaches.

# ACCOLATE helps achieve the NIH goals of asthma therapy

| Goal[17] | How ACCOLATE Helps |
|---|---|
| • Prevent chronic and troublesome symptoms | • Improves daytime asthma symptom scores[3]<br>• Reduces nighttime awakenings[3]<br>• Reduces $\beta_2$-agonist use[4] |
| • Maintain (near) "normal" pulmonary function | • Improved ($P<0.01$) $FEV_1$ in a 6-week clinical trial (n=276)[5]<br>• Improved ($P<0.05$) $FEV_1$ and morning PEF in a 13-week clinical trial (n=762)[6]<br>• In single-dose challenge studies, ACCOLATE reduced effects of common environmental triggers |
| • Maintain normal activity levels | • In a 13-week trial, more symptom-free days ($P=0.0348$)[7]* and more problem-free days ($P=0.0002$)[7]† |
| • Provide optimal pharmacotherapy with minimal or no adverse effects | • Generally well tolerated in clinical studies; side effects include headache (12.9%),[8] infection (3.5%),[9] and nausea (3.1%) |
| • Meet patient and family expectations of and satisfaction with asthma care | • In a clinical trial, preferred 2:1 over metered-dose inhaler therapy (ACCOLATE 55% vs beclomethasone 27%)[13] |
| • Prevent recurrent exacerbations of asthma and minimize the need for emergency department visits or hospitalizations[14,15] | • Reduced the risk of requiring oral steroids for asthma exacerbations by 50% across five 13-week trials in a meta-analysis[16] |

*The mean % of days for which the daytime asthma symptom score was 0 (no symptoms).

†The mean % of days for which the daytime asthma symptom score was ≤1 (mild symptoms that did not interfere with activities).

‡In clinical trials, an increased proportion of patients taking ACCOLATE over the age of 55 years reported infections as compared to placebo-treated patients. Infections were generally mild to moderate and predominantly of the respiratory tract.

ACCOLATE should be used during pregnancy only if clearly needed. ACCOLATE should not be administered to mothers who are breast-feeding.

Rare cases of increased theophylline levels after the addition of ACCOLATE to an existing theophylline regimen have been reported. The mechanism of interaction in these patients is unknown, but physicians should exercise prudence when coadministering ACCOLATE and theophylline.

Patients should not modify any of their antiasthma medications unless instructed by a doctor.

Patients on oral warfarin anticoagulant therapy and ACCOLATE should have their prothrombin times monitored and anticoagulant dose adjusted accordingly.

If clinical signs or symptoms of liver dysfunction are noted, it is reasonable to recommend standard liver tests be performed and the patient managed accordingly.[9]

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