DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-547/S-014

AstraZeneca LP
1800 Concord Pike
P.O.Box 8355
Wilmington, Delaware 19803-8355

Attention: Eric Couture, Ph.D.
Director, Regulatory Affairs

Dear Dr. Couture:

Please refer to your supplemental new drug application dated June 29, 2000, received June 30, 2000, 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 submissions dated January 22 and April 25, 2001.

This supplemental new drug application provides for the use of Accolate 10 mg for the prophylaxis and chronic treatment of asthma in pediatric patients 5 - 6 years of age.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text and with the minor editorial revisions listed below. Accordingly, the supplemental application is approved effective on the date of this letter.

1. Revise the first paragraph of the "Carcinogenesis, Mutagenesis, Impairment of Fertility" subsection of the PRECAUTIONS section to read as follows.

> **Carcinogenesis, Mutagenesis, Impairment of Fertility:** In two-year carcinogenicity studies, zafirlukast was administered at dietary doses of 10, 100 and 300 mg/kg to mice and 40, 400 and 2000 mg/kg to rats. Male mice at an oral dose of 300 mg/kg/day (approximately 30 times the maximum recommended daily oral dose in adults and in children on a mg/m^2 basis) showed an increased incidence of hepatocellular adenomas; female mice at this dose showed a greater incidence of whole body histocytic sarcomas. Male and female rats at an oral dose of 2000 mg/kg/day (resulting in approximately 160 times the exposure to drug plus metabolites from the maximum recommended daily oral dose in adults and in children based on a comparison of the

plasma area-under the curve [AUCs] values) of zafirlukast showed an increased incidence of urinary bladder transitional cell papillomas. Zafirlukast was not tumorigenic at oral doses up to 100 mg/kg (approximately 10 times the maximum recommended daily oral dose in adults and in children on a mg/m^2 basis) in mice and at oral doses up to 400 mg/kg (resulting in approximately 140 times the exposure to drug plus metabolites from the maximum recommended daily oral dose in adults and in children based on a comparison of the plasma [AUCs] values) in rats. The clinical significance of these findings for the long-term use of ACCOLATE is unknown.

2. Revise the "Pregnancy Category "subsection of the PRECAUTIONS section to read as follows.

Pregnancy Category B: No teratogenicity was observed at oral doses up to 1600mg/kg/day in mice (approximately 160 times the maximum recommended daily oral dose in adults on a mg/m^2 basis), up to 2000 mg/kg/day in rats (approximately 410 times the maximum recommended daily oral dose in adults on a mg/m^2 basis) and up to 2000 mg/kg/day in cynomolgus monkeys (which resulted in approximately 20 times the exposure to drug plus metabolites compared to that from the maximum recommended daily oral dose in adults based on comparison of the AUCs values). At an oral dose of 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 the maternally toxic oral dose of 2000 mg/kg/day. There are no adequate and well-controlled trials in pregnant women. Because animal reproductive studies are not always predictive of human response, ACCOLATE should be used during pregnancy only if clearly needed.

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted draft labeling (package insert submitted April 25, 2001). These revisions are terms of the approval of this application.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no 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-014." Approval of this submission by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR

314.55 (or 601.27). We are deferring submission of your pediatric studies until May 31, 2003. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" 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,

{See appended electronic signature page}

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