CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-547/S007

ADMINISTRATIVE DOCUMENTS

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 20547/007
Stamp: 18-SEP-1998
Regulatory Due: 18-SEP-1999
Applicant: ZENECA
1800 CONCORD PIKE
WILMINGTON, DE 198505437
Priority: 1S
Org Code: 570

Action Goal:
District Goal: 14-AUG-1999
Brand Name: ACCOLATE (ZAFIRLUKAST) ORAL TABS 20MG
Estab. Name:
Generic Name: ZAFIRLUKAST

Dosage Form: (TABLET)
Strength: 20 MG

Application Comment:
FDA Contacts: P. JANI (HFD-570) 301-827-1050 , Project Manager
ID = 100963 , Review Chemist
G. POOCHIKIAN (HFD-570) 301-827-1050 , Team Leader

Overall Recommendation: ACCEPTABLE on 26-OCT-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 2650168
IPR PHARMACEUTICALS INC
SOUTH MAIN ST
CAROLINA, PR 009841967

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
Profile: TCM OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	02-OCT-1998				LEAK
SUBMITTED TO DO	02-OCT-1998	10D			COOKK
DO RECOMMENDATION	26-OCT-1998			ACCEPTABLE	CROSA
				BASED ON FILE REVIEW	
APPROVAL IS RECOMMENDED BASED ON THE LAST TCM PROFILE INSPECTION OF 3/27/97, WHICH WAS FOUND TO BE ACCEPTABLE.					
OC RECOMMENDATION	26-OCT-1998			ACCEPTABLE	DAMBROGIOJ
				DISTRICT RECOMMENDATION	

Establishment: 2650183
IPR PHARMACEUTICALS INC
STATE ROAD 53 KM 84
GUAYAMA, PR 00784

DMF No: AADA:
Responsibilities: FINISHED DOSAGE STABILITY TESTER
Profile: CTL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	02-OCT-1998				LEAK
OC RECOMMENDATION	02-OCT-1998			ACCEPTABLE	COOKK
				BASED ON PROFILE	

Establishment: 2517100
ZENECA PHAMACEUTICALS
587 OLD BALTIMORE PIKE
NEWARK, DE 19702

DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Profile: TCM OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	02-OCT-1998				LEAK
SUBMITTED TO OC	02-OCT-1998				LEAK
OC RECOMMENDATION	02-OCT-1998			ACCEPTABLE BASED ON PROFILE	COOKK

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 20547/007
Stamp: 18-SEP-1998 Regulatory Due: 18-SEP-1999
Applicant: ZENECA
1800 CONCORD PIKE
WILMINGTON, DE 198505437

Priority: 1S Org Code: 570
Action Goal: District Goal: 14-AUG-1999
Brand Name: ACCOLATE (ZAFIRLUKAST) ORAL TABS 20/40MG
Established Name:
Generic Name: ZAFIRLUKAST
Dosage Form: TAB (TABLET)
Strength: 20 MG

FDA Contacts:

P. JANI	(HFD-570)	301-827-1050	, Project Manager
J. LEAK	(HFD-570)	301-827-1050	, Review Chemist
G. POOCHIKIAN	(HFD-570)	301-827-1050	, Team Leader

Overall Recommendation:

ACCEPTABLE on 26-OCT-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 2650168
IPR PHARMACEUTICALS INC
LA CERAMICA INDUSTRIAL PARK
SOUTH MAIN ST
CAROLINA, PR 009841967
DMF No:
AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 26-OCT-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Establishment: 2650183
IPR PHARMACEUTICALS INC
STATE ROAD 53 KM 84
GUAYAMA, PR 00784
DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 02-OCT-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Establishment: 2517100
ZENECA PHAMACEUTICALS
587 OLD BALTIMORE PIKE
NEWARK, DE 19702
DMF No:
AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 02-OCT-1998

Responsibilities: FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

APPEARS THIS WAY
ON ORIGINAL

Zeneca Pharmaceuticals,
A Business Unit of Zeneca Inc.
Drug Regulatory Affairs Department
Wilmington, DE 19850-5437

ACCOLATE® (zafirlukast) Tablets
NDA 20-547

ITEM 13: Pursuant to Section 505 of the Federal Food, Drug and Cosmetic Act, the attached information following below is made of record.

A. PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG OR A METHOD OF USING THE DRUG

CERTIFICATION

Pursuant to 21 CFR section 314.53(d)(2)(ii), Zeneca Ltd., through its Agent Zeneca Pharmaceuticals, a Business Unit of Zeneca Inc. (hereinafter for this Item 13, "Zeneca Pharmaceuticals") certifies that U.S. Patent Nos. 4,859,692; 5,294,636; 5,319,097; 5,482,963; and 5,583,152, information relative to each of which has previously been submitted, claim the change in ACCOLATE® (zafirlukast) Tablets which is the subject of this supplemental new drug application.

Richard A Elder

RICHARD A. ELDER
CHIEF IP COUNSEL
PHARMACEUTICALS

APPEARS THIS WAY
ON ORIGINAL

NOTE: **The submitted clinical data alone would not support approval of this supplemental application for use of Accolate in children [redacted] - 11 years of age. The determination to approve this supplemental application for the age group 7 - 11 years is made based on supportive pharmacokinetics data. Additional pharmacokinetics data would be required, before this product could be approved for children [redacted] years of age.**

/S/

Signature
Title: Project Manager

9-17-99

Date

/S/

Signature of Office/
Division Director

9/17/99

Date

cc: Original NDA 20-547
Division File/HFD-570
HFD-570/Jani
HFD-93 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

B. EXCLUSIVITY INFORMATION

1. Exclusivity Claim

Zeneca Pharmaceuticals claims an exclusivity period of three years for the change in ACCOLATE® (zafirlukast) Tablets presented in this supplemental new drug application.

Zeneca Pharmaceuticals also claims all applicable six month exclusivity extensions provided under the Pediatric Studies of Drugs provisions of the Food and Drug Administration Modernization Act of 1997.

2. Authority for Exclusivity Claim

Exclusivity for the change in ACCOLATE® (zafirlukast) Tablets presented in this supplemental new drug application is being claimed pursuant to 21 CFR Section 314.108(b)(5) and 21 USC 355A(c).

3. Information Demonstrating this Supplemental Application Contains New Clinical Investigations Conducted or Sponsored by the Applicant that are Essential to the Approval of this Supplemental New Drug Application.

a. Certification of New Clinical Investigations

Zeneca Pharmaceuticals certifies that to the best of Zeneca Pharmaceuticals' knowledge, each of the clinical investigations included in this supplemental new drug application meets the definition of "new clinical investigation" set forth in 21 CFR Section 314.108(a).

Catherine M. Bonuccelli, m.d.

CATHERINE M. BONUCCELLI, M.D.
MEDICAL DIRECTOR

APPEARS THIS WAY
ON ORIGINAL

b. Essential to Approval

(i) Literature Search

Attached as Exhibit A is a list of all published studies and publicly available reports of clinical investigations known to Zeneca Pharmaceuticals through a literature search that are relevant to the conditions for which Zeneca Pharmaceuticals is seeking approval.

(ii) Certification

Zeneca Pharmaceuticals certifies that Zeneca Pharmaceuticals has thoroughly searched the scientific literature and, to the best of Zeneca Pharmaceuticals' knowledge, the list of relevant published studies and/or publicly available reports is complete and accurate, and in Zeneca Pharmaceuticals' opinion, such published studies and/or publicly available reports do not provide a sufficient basis for the approval of the conditions for which Zeneca Pharmaceuticals is seeking approval without reference to the new clinical investigation(s) in this supplemental new drug application.

Catherine M. Bonuccelli, M.D.

CATHERINE M. BONUCCELLI, M.D.
MEDICAL DIRECTOR

(iii) Explanation

The listed published studies and/or publicly available reports of clinical investigations do not provide sufficient basis for the approval of the conditions for which Zeneca Pharmaceuticals is seeking approval, without reference to the new clinical investigations in this supplemental new drug application.

APPEARS THIS WAY
ON ORIGINAL

b. Essential to Approval

(i) Literature Search

Attached as Exhibit A is a list of all published studies and publicly available reports of clinical investigations known to Zeneca Pharmaceuticals through a literature search that are relevant to the conditions for which Zeneca Pharmaceuticals is seeking approval.

(ii) Certification

Zeneca Pharmaceuticals certifies that Zeneca Pharmaceuticals has thoroughly searched the scientific literature and, to the best of Zeneca Pharmaceuticals' knowledge, the list of relevant published studies and/or publicly available reports is complete and accurate, and in Zeneca Pharmaceuticals' opinion, such published studies and/or publicly available reports do not provide a sufficient basis for the approval of the conditions for which Zeneca Pharmaceuticals is seeking approval without reference to the new clinical investigation(s) in this supplemental new drug application.

Catherine M. Bonuccelli, M.D.

CATHERINE M. BONUCCELLI, M.D.
MEDICAL DIRECTOR

(iii) Explanation

The listed published studies and/or publicly available reports of clinical investigations do not provide sufficient basis for the approval of the conditions for which Zeneca Pharmaceuticals is seeking approval, without reference to the new clinical investigations in this supplemental new drug application.

APPEARS THIS WAY
ON ORIGINAL

Zeneca Pharmaceuticals believes that the published studies and/or publicly available reports listed in Exhibit A hereto do not provide sufficient basis for the approval of the conditions for which Zeneca is seeking approval within this supplemental new drug application for ACCOLATE® (zafirlukast) Tablets . The listed published studies and/or publicly available reports of clinical investigations do not contain sufficient information for the following reasons:

There are no published reports of the use of ACCOLATE as treatment for chronic asthma in children under the age of 12 years, nor is there published information on the pharmacokinetics or pharmacodynamics of ACCOLATE in this age group. Although it is appropriate to extrapolate efficacy data in adults with asthma to the pediatric population, this can only be done in the context of adequate information on pharmacokinetics and dose selection in children.

c. Conducted or Sponsored by the Applicant.

Zeneca Pharmaceuticals, A Business Unit of Zeneca Inc., the agent and a wholly-owned subsidiary of Zeneca Ltd., is the sponsor named in form FDA-1571 for IND [redacted] under which the new clinical investigations essential to the approval of this supplemental new drug application were conducted. We believe this fact is sufficient under 21 CFR 314.50(j)(4)(iii) to establish that the clinical investigations were conducted or sponsored by the Applicant.

APPEARS THIS WAY
ON ORIGINAL

EXHIBIT A

APPEARS THIS WAY
ON ORIGINAL

Knorr B, Matz J, Bernstein JA, Nguyen H, Seidenberg BC, Reiss TF. Montelukast for Chronic Asthma in 6- to 14-Year-Old Children. Journal of the American Medical Association 1998; 279 (15):1181-1186, 1998.

Knorr BA, Matz J, Sveum RJ, Becker AB, Reiss TF, Seidenberg BC, Nguyen H. Montelukast (MK-0476) improves asthma over 6 months of treatment in 6- to 14- year old patients. European Respiratory Journal 1997; 10 Suppl 25: 219S Abs P1429.

Ostrom N, Bronsky E, Pearlman D, Hanby L, Bonuccelli C. Effects of the leukotriene-receptor antagonist zafirlukast on exercise-induced asthma in pediatric subjects. European Respiratory Journal 1997; 10 Suppl 25: 276S Abs P1808.

Knorr BA, Matz J, Bernstein JA, Becker A, Reiss TF, Friedman B, Erickson U, Nguyen H. Montelukast (MK-0476) improves asthma over a 2 month treatment period in 6- to 14- year olds. American Journal of Respiratory and Critical Care Medicine 1997; 155(4) Part 2: A664 Abs.

Kemp JP, Dockhorn RJ, Shapiro GG, Nguyen HH, Guerreiro DA, Reiss TF, Friedman BS, Knorr BA. Montelukast, a leukotriene receptor antagonist, inhibits exercise-induced bronchoconstriction in 6- to- 14- year old children. Journal of Allergy and Clinical Immunology 1997; 99 (1) Part 2: S321 Abs 1314.

Pearlman DS, Ostrom NK, Bronsky EA, Hanby LA, Bonuccelli CM. Efficacy and safety of zafirlukast (ACCOLATE) in pediatric patients with exercise-induced asthma. Annals of Allergy, Asthma and Immunology 1997; 78 (1): 113 Abs P43.

Spahn JD; Szefler SJ. Pharmacologic management of pediatric asthma. Immunology and Allergy Clinics of North America (United States) 1998; 18 (1): 165-181.

Knorr B, Nguyen H, Villaran C, Kearns G, Boza M, Rogers J, Reiss T, Spielberg S. Selection of a montelukast dose in 2- to 5-year-olds by a comparison of pediatric and adult single-dose population pharmacokinetic (PK) profiles. Clinical Pharmacology and Therapeutics 1998; 63 (2): Abs PII74-PII74.

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20547	**Trade Name:**	ACCOLATE (ZAFIRLUKAST) ORAL TABS 20MG
Supplement Number:	7	**Generic Name:**	ZAFIRLUKAST
Supplement Type:	SE1	**Dosage Form:**	Tablet; Oral
Regulatory Action:	PN	**Proposed Indication:**	This supplemental new drug application provides for the use of Accolate 10 mg for the prophylaxis and chronic treatment of asthma in pediatric patients 7 - 11 years of age.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Adequate for SOME pediatric age groups
Formulation Status	NO NEW FORMULATION is needed
Studies Needed	STUDIES needed. Applicant in NEGOTIATIONS with FDA
Study Status	Protocols are submitted and under review

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

9-17-99: The supplement will be approved today. The sponsor has submitted the clinical studies for children 7-11 years of age but there are not enough efficacy data to determine appropriate dose for children 2-6 years of age. The decision to approve this supplement for children 7 -11 years of age is made based on supportive PK data, and invoking the Pediatric Rule.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, PARINDA JANI

/S/

Signature

9-17-99

Date

ZENECA
Pharmaceuticals Group
ZENECA Pharmaceuticals / Stuart Pharmaceuticals
Business Units of ZENECA Inc

1800 Concord Pike
Wilmington
Delaware 19897 USA

Telephone (302) 886-2132
Fax (302) 886-2822

William J. Kennedy, Ph.D.
Vice President
Drug Regulatory Affairs Department

SEP 17 1998

Re: ACCOLATE® (zafirlukast) sNDA (Pediatric Use)

In response to the requirements of the Generic Drug Enforcement Act of 1992, I hereby certify on behalf of Zeneca Pharmaceuticals, a Business Unit of Zeneca Inc., that we did not and will not use in connection with this application, the services of any person in any capacity debarred under section 306 (a) or (b).

Sincerely,

William J. Kennedy, Ph.D.

WJK/DAG/car

APPEARS THIS WAY
ON ORIGINAL

Division Director's Memorandum

Date: Thursday, September 16, 1999
NDA: 20-547; efficacy supplement S-007
Sponsor: AstraZeneca
Proprietary Name: Accolate (zafilukast) tablets

Introduction: This is a supplemental NDA for Accolate tablets to seek approval for the prophylaxis and treatment of chronic asthma in children between the ages of [ ] 11 (currently Accolate is approved down to age 12). It also proposes [ ] new dosage strengths – [ ] and 10 mg tablets, in addition to the approved 20 mg product.

CMC: The CMC review reveals both of the new tablets to be approvable from the CMC standpoint. The pharmaceutics of the tablets are very similar and proportional to the 20 mg tablets, except for the dosage strength itself.

Pharmacology/toxicology: No new issues, given the lower age range proposed is [ ] and above. Labeling multiples of human dosage will need to be revised as appropriate (i.e., other than reproductive and pregnancy sections).

Biopharmaceutics review: Dr. Hunt did the primary review. Essentially, the sponsor has provided evidence that children aged 7 – 11 years have double the exposure compared to adults when both populations are exposed to 20 mg dosing (the PK studies failed to enroll in the [ ] year old age group). Given zafirlukast's linear kinetics in the relevant range, this means that a 10 mg dose would be expected to give comparable exposures to children in this age range compared to adults. It is notable that there was at least a signal in the 7-year old data that these younger children may have lower clearances than that seen on average in older children.

There were sparse serum samplings done in the pivotal clinical studies. However, since these samplings were not done at set times post-dosing in a consistent manner between patients, the data do not characterize the resultant PK profiles sufficiently to allow any population-based conclusions to be drawn. Therefore, the sponsor has not provided adequate, interpretable PK information in the [ ] year olds.

Finally, there are also reasonable pharmaceutics (including in vitro dissolution data) and PK data to feel that the three dosage strengths would provide comparable exposure if administered at the same nominal dose.

Clinical / Stastical: Drs. Anthracite and Gebert reviewed the pivotal studies for this indication (see these primary reviews for details). The two studies included a study 0079 – a study of Accolate dosed at [ ] and 10 mg twice daily dosing in children ages [ ] –11 for 4 weeks, and a second study, 0139, of 10, 20 and 40 mg twice daily in the same population for 6 weeks. Although there were clear trends for active drug being numerically better than placebo, no consistent statistical separation was found for any dose and on any measure of efficacy. Frequently there was either no dose ordering of apparent effect, or a reverse dose-ordering.

These studies failed to demonstrate efficacy of any dose, and also failed to identify themost appropriate dose(s). It should be noted that the effect size seen in these pediatric

studies does not greatly differ from that seen in adolescents and adults. If these studies under consideration were comparably large as the adult studies, they may well have shown more convincing statistical results. This in part speaks to the rather modest efficacy of this agent, however, since the pediatric studies had in excess of 100 patients per arm, which for trials of corticosteroids in asthma has proven to be more than adequate power.

The clinical studies submitted, as well as an open label extension, did provide reasonable evidence of short to medium term safety, with results comparable to that seen in clinical trials in adults.

Auditing / Data Checking: The Division elected not to request routine DSI audits of these studies due to the known efficacy of this agent. No circumstances that would have elicited a "for cause" audit were discovered in the review (note that Dr. Edwards, who's data has otherwise been questioned, did participate in this program, but the data were disregarded). The medical officer and statisticians performed their own auditing/checking of the data and did not identify any crucial problems that would invalidate the study conclusions.

EERS: Acceptable EERs are in place for the finished dosage manufacturer (IPR pharm. in Puerto Rico), for the stability testing facility (IPR, in Puerto Rico) and for the final dosage packer / releaser (Zeneca, Newark DE). The overall EER is date 10-26-1998.

Labeling: The labeling as proposed needs to be amended to restrict the approval to 7 – 11 year olds, and to remove reference to the [redacted] tablet (see below). Additionally, mentions of hepatic transplants and deaths should be added, and references to [redacted] and [redacted] will be removed. Other modifications as recommended by the Pharm/Tox and Biopharm reviewers will be implemented.

Conclusions: The sponsor failed to provide adequate clinical evidence of efficacy for Accolate in the [redacted]-11 year old age group, nor did these data identify the optimal dose. However, the clinical trials data so support that a treatment effect *might* be expected and that the treatment effect in children of this age would be in the range of that seen in adults. Therefore, it is reasonable to invoke the Pediatric Rule which allows for PK data to be used to establish the effective dose for pediatrics *if the disease is substantially the same in adults and children and the response to the drug is expected to be substantially the same in the two populations*. DPADP has already accepted the former for asthma, and the clinical data submitted at least support the latter conclusion. Therefore, an approval for 10 mg twice daily in treating patients 7 – 11 years of age can be based on the PK data, along with the clinical safety data from the pivotal trials and open-label extension. However, since these data only come from patients down to age 7 and the lower aged children tended towards lower clearances, it is not clear what the appropriate dose for the [redacted] year old age range would be. A discussion was held with the sponsor over the Division's review conclusions, and they elected to amend the supplement to withdraw the [redacted] dosage strength and the indication for the [redacted] year olds and gain approval for the 7 – 11 year olds, rather than to face less than an approval for the supplement as submitted. The [redacted] tablet, which is otherwise approvable, will be approved when and if a population of users for that strength is identified. The sponsor

has committed to providing specific PK data to identify an appropriate dose in the [redacted] year old patient population.

/S/

Robert J. Meyer, MD
Director,
Division of Pulmonary and Allergy Drug Products.

9/15/99

APPEARS THIS WAY
ON ORIGINAL