CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-547/S007

CORRESPONDENCE

Memorandum of Telephone Facsimile Correspondence

Date: September 14, 1999

To: Mark DeSiato
Regulatory Affairs

From: Parinda Jani
Project Manager

Through: Ramana Uppoor, Ph.D. /S/ 09/14/99
Biopharmaceutics and Clinical Pharmacology Team Leader

Subject: Comments for NDA 20-547/S-007/Accolate Tablets

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

Regarding the revised package insert that was submitted September 10, 1999, address the following related to the CLINICAL PHARMACOLOGY:Pharmacokinetics section.

1. Provide the source for the 45 % value for the statement "Accumulation of zafirlukast in the plasma following twice daily dosing is approximately 45%." This value seems to be an overestimation based upon a comparison of Day 14 AUC (0-12) to Day 1 AUC (0-12) that is now included as a table in the package insert for the adult pharmacokinetic parameters.

2. The current table for the adult PK parameters includes values from a study where [redacted] doses were administered. It would be better to provide PK parameters from a study that administered the approved 20 mg dose. Therefore, the PK parameters from the study 9188IL/0144 that utilized the 10 mg to-be-marketed tablet for the 20 mg dose, should replace the currently provided values.

3. Revise the subsection titled "Children" under CLINICAL PHARMACOLOGY: Special Populations as follows:

   "Children: Following administration of a 20 mg dose of zafirlukast to 20 boys and girls between 7 and 11 years of age, a mean (%coefficient of variation) peak drug concentration of 601 ng/mL (45%) was obtained at about 2.5 hrs. Zafirlukast systemic exposure as determined by mean AUC was 2027 ng.h/mL (38%). Weight unadjusted apparent clearance was 11.4L/h (42%) which resulted in greater systemic drug exposure that that obtained in adults for an identical dose. Zafirlukast disposition was unchanged after multiple dosing (20 mg twice daily) in children and the degree of accumulation in plasma was similar to that observed in adults."

Additional labeling comments will be forthcoming.

Memorandum of Telephone Facsimile Correspondence

Date: September 8, 1999

To: Mark DeSiato
Regulatory Affairs

From: Parinda Jani
Project Manager

Through: Ramana Uppoor, Ph.D. /S/ 9/8/99
Biopharmaceutics and Clinical Pharmacology Team Leader

Subject: Comments for NDA 20-547/S-007/Accolate Tablets

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

APPEARS THIS WAY
ON ORIGINAL

1. Currently, an attempt is being made to standardize the content and presentation of information that is to be given in the Clinical Pharmacokinetics section of the package insert. For this section there should be subheadings with appropriate information for the Absorption, Distribution, Metabolism, and Excretion. Following this, there should be a section with the heading of Special Populations and appropriate subheadings (e.g., Geriatrics, Pediatrics, Hepatic Insufficiency, Renal Insufficiency, etc., as appropriate). Lastly, a table with mean (± SD) pharmacokinetic parameters for single dose and steady state conditions should be provided. Therefore, please modify your package insert as noted.

2. The currently approved in vitro dissolution method for the 20 mg tablet is acceptable for the and 10 mg tablets. (i.e., except that the acceptance specifications should be changed to Q = in minutes for all three tablet strengths.

APPEARS THIS WAY
ON ORIGINAL

Memorandum of Telephone Facsimile Correspondence

Date: August 17, 1999

To: Mark DeSiato
Regulatory Affairs

From: Parinda Jani
Project Manager

Through: Ramana Uppoor, Ph.D. /S/ 8/17/99
Team leader, Biopharmaceutics and Clinical Pharmacology

Subject: Comments for NDA 20-547/S-007

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

"Since ACCOLATE is approved for marketing outside the U.S., is it approved for children between the ages of [redacted] years? If so, what is the recommended dosing regimen for this age group? If there are different approved dosing regimens for different countries for this age range, what are they and how long have they been in use. If there is a different dosing regimen(s) approved in a foreign country(ies) that differs from the one being proposed for the U.S., please provide the rational for the difference in the dosing regimen(s). Lastly, are there any countries where approval of ACCOLATE for ages [redacted] years is pending, and if so, what is the proposed dosing regimen(s). Again, if the dosing regimen(s)differs from the one being proposed for the U.S. please provide the rational for the difference."

APPEARS THIS WAY
ON ORIGINAL

MESSAGE CONFIRMATION

Memorandum of Telephone Facsimile Correspondence

Date: August 6, 1999

To: Mark DeSiato
Regulatory Affairs

From: Parinda Jani
Project Manager

Through: Ramana Uppoor, Ph.D. /S/ 8/6/99
Team leader, Biopharmaceutics and Clinical Pharmacology

Subject: Comments for NDA 20-547/S-007

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

On page 86 of Volume 7.1 of the September 17, 1998, supplemental NDA submission are Figures 2-1A and 2-1B. Please provide the study numbers from which the data were obtained for the plotted results for children (n=18), adolescents (n=19) and adults (n=304). Since it is assumed that the plotted results for children only come from Study No. 9188IL/0058, it is requested that new data analyses be done to include the newly obtained clearance information for this age group (i.e., from Study No. 9188IL/0145). Similarly for the adult data, if the presented results do not include the findings from Study Nos. 9188IL/0144 and 9188IL/0152, new data analyses should be done to include them. For the adolescent age group (n=19) is it correct that all the available data has been included in the presented data analyses? Lastly, please provide the numerical values for what is presented in the current figures in table form, as well as the numerical values from the new data analyses.

RECORD OF TELEPHONE CONVERSATION

NDA: #20-547 Supplement 7 DATES: 7/27 - 8/6/99

INITIATED BY: __APPLICANT _XX_FDA

FIRM NAME: Zeneca

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD:
Mary Wheley, Mark DeSiato (at various times)

TELEPHONE NUMBER: (302)886-8510

7/27/99 I called, got Mary Wheley and asked in Trial 139 what End Week 3 refered to since no data was collected at week 3, but was at Visit 3 randomization). I also asked what values for the last two efficacy parameters served as baseline.

7/28/99 Mark DeSiato left a voice mail message to answer the preceding questions:

Day #0 = end run-in period = randomization
End Week 3 = End Double-Blind Week 3 = Visit 4 = Flow Chart Week 5

7/30/99 I called Mark about similar notation for Trial 079 and he confirmed that corresponding tabular references to 'weeks' referred to the double-blind weeks. I asked about CRF's which he said were submitted as a part of the Acrobat text imaging files. Specifically, the start-up file is SUPPLETOC.PDF, which should have hotlinks to DPTOC.PDF, which was part of the original submission. Additional files include AMENDTC1.PDF, which has CRF's for Trial 0139, and AMENDTC2.PDF, with the 4-Month Safety Update.

I could find none of the last three files on the network drive [redacted] and I tried searching all of that network drive for those named files without success. Later Jim Gebert (statistician) showed me that they were on the INTRANET under the Electronic Document Room (EDR).

8/6/99 I called Mark about locating the Asthma Diary card in the hard copy. He returned the call and referenced it in the 11/19/98 submission Vol 9 Page 57 (Appendix E), also in section 7.2.7 of the final protocol in Vol 9 Pages 36-7 (Appendix D).

/S/

Raymond F. Anthracite, M.D.
Medical Review Officer

cc:
NDA #20-547 Supplement 7
HFD-570/Division File
HFD-570/Team Leader/Chowdhury
HFD-570/Medical Reviewer/Anthracite
HFD-570/PM/Jani

APPEARS THIS WAY
ON ORIGINAL

NDA 20-547/S-007

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

DEC 23 1998

Attention: Mark Desiato
Senior Regulatory Specialist
Marketed Products
Drug Regulatory Affairs Department

Dear Mr. Desiato:

Please refer to your pending September 17, 1998, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Accolate (zafirlukast) 20 mg Tablets.

We have initiated our review of the Pharmacokinetics section of your submission and have the following comments and information requests.

1. Provide formulation composition as well as dissolution profiles on the different tablet strengths used in the study 0058. Provide the formulation composition and dissolution profiles of the currently approved 20 mg tablets as a comparison.

2. Provide the plasma concentration time data as well as PK parameters electronically for all the PK studies.

3. Calculate the clearance and volume of distribution values for study 0145 and provide a comparison of the PK parameters to that of adults and adolescents.

4. Provide dissolution profiles on the 10 mg and [redacted] Phase 3 clinical tablet formulations.

5. Provide dissolution profile data on 12 tablets per lot (individual values of % dissolved) for the two new tablet strengths (to-be-marketed bio-batches) in three different dissolution media and your rationale for selection of the proposed dissolution conditions.

We would appreciate your prompt written response so we can continue our evaluation of your supplemental application.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Parinda Jani, Project Manager, at (301) 827-1064.

Sincerely yours,

Cathie Schumaker, R.Ph.
Chief, Project Management Staff
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

23 **Page(s) Redacted**

Draft

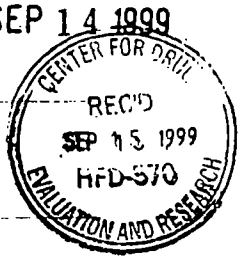
Labeling

ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.

1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

DESK COPY

SEP 14 1999



SENT VIA RAPIFAX AND
UPS NEXT DAY AIR

Dr. Robert Meyer
Division Director
Division of Pulmonary
Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Office of Drug Evaluation II
HFD No. 570, Room 10B-03
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Meyer:

Re: ACCOLATE® (zafirlukast) Tablets
NDA 20-547
ACCOLATE Pediatrics sNDA (Supplement-007);
Supplement to a Pending Application: Change in Indication; Withdrawal of [redacted]
Dosage, Change in Dissolution Specifications

Reference is made to the September 17, 1998 submission of the supplemental New Drug Application (S-007) for the use of ACCOLATE® (zafirlukast) Tablets in the Prophylaxis and Chronic Treatment of Asthma in Pediatric Patients [redacted] years of age.

Reference is made to teleconferences held between the Division and Zeneca Pharmaceuticals on September 10, 1999 and September 13, 1999. Following the outcome of these teleconferences Zeneca hereby agrees to amend the above mentioned sNDA in the following manner:

- The indication will be changed from:

[redacted]

to:

"ACCOLATE is indicated for the Prophylaxis and Chronic Treatment of Asthma in adults and children 7 years of age and older"

APPEARS THIS WAY
ON ORIGINAL

- [redacted] The 10 mg (bid) dosage will remain for use in pediatric patients 7 to 11 years of age.

- The tablet dissolution specifications will be changed as follows:

  Beginning October 1, 1999, ACCOLATE 10 mg tablets will be released according to the new dissolution specification of Q = [redacted] at [redacted] minutes. The currently approved ACCOLATE 20 mg tablets will be released according to the new dissolution specification (Q = [redacted] at [redacted] minutes) beginning January 1, 2000. All product released prior to the above mentioned dates will be released according to the current dissolution specification of Q = [redacted] at [redacted] minutes. All product currently on stability will maintain the current tablet dissolution specification of Q = [redacted] at [redacted] minutes. All product put on stability after the above implementation dates (October 1, 1999 for 10 mg tablets; January 1, 2000 for 20 mg tablets) will be tested against the new dissolution specification of Q = [redacted] at [redacted] minutes.

Furthermore, pursuant to Zeneca's discussion with the Division on September 13, 1999, Zeneca plans to seek approval of ACCOLATE for the [redacted]

If you have any questions or require additional information, please do not hesitate to contact me.

Sincerely,

/S/

Mark A. DeSiato
Senior Regulatory Specialist
Marketed Products
Regulatory Affairs Department
(302) 886-8510
(302) 886-2822 (fax)

MAD/gem

Desk Copies: Ms. Parinda Jani, HFD No. 570, Room 10B-45 (Desk Copy)

APPEARS THIS WAY
ON ORIGINAL

TEAM LEADER MEMORANDUM

DATE: September 14, 1999

TO: NDA 20-547

/S/ 9/14/99

FROM: Badrul A. Chowdhury, MD, PhD
Acting Team Leader, Division of Pulmonary and Allergy Drug Products

SUBJECT: Secondary medical review of zafirlukast (Accolate®) pediatric supplement

CC: HFD-570: Meyer, Anthracite, Uppoor, Jani,

Administrative

NDA 20-547 pediatric efficacy supplement for zafirlukast was submitted by Zeneca Pharmaceuticals on September 17, 1998. The user fee goal date for completion of this application review is September 18, 1999. Zafirlukast was approved for prophylaxis and chronic treatment of asthma in patients 12 years of age and older on September 26, 1996. The recommended dose for patients 12 years and older is 20 mg by mouth BID. The sponsor now submits this application to obtain the same indication for patients [redacted] through 11 years of age. The proposed starting dose for this age group is [redacted] mg by mouth BID, with a statement that the dose may be increased to 10 mg BID for poorly controlled asthma.

Clinical studies

The sponsor has submitted results from two large studies in 5 to 11 year old children with asthma. The studies are 0079 and 0139. In addition, one small, crossover, challenge study in 6 to 14 year old children with exercise-induced bronchospasm was also submitted. This review will focus on the two asthma studies, since zafirlukast is not indicated for exercise-induced bronchospasm. Furthermore, the two asthma studies are more informative. Details of these studies can be found in Dr. Anthracite's excellent medical review.

Study 0079 was a three-arm, 1:1:1 randomized, multicenter, double-blind, placebo-controlled, dose-ranging, parallel-group study in patients 5 to 11 years of age with mild-to-moderate asthma (FEV_1 50-90% of predicted). The study included 4 periods: a 1-week screening period, a 7-10 day single-blind placebo run-in period, a 4-week double-blind period, and an optional 52-week open-label safety extension period. A total of 311 patients were randomized and 288 patients completed the study. During the randomization period, patients were treated with placebo or zafirlukast (5 or 10 mg BID). In the open-label period, patients were treated with zafirlukast 10 mg BID. Patients were allowed to enter the open-label portion of the study either from the double-blind period or directly from the screening period without participating in the double-blind period. Various measures of efficacy were assessed, without a predefined primary efficacy variable. These included percent predicted

FEV_1, absolute FEV_1, PEFR, asthma symptom score, beta-2 agonist use, school absenteeism, medical contact for asthma, and withdrawal due to asthma. Absolute FEV_1 was used to calculate the sample size. Statistical significance in this study has a limited value. With this limitation, statistical significance was seen for FEV_1 percent predicted in the 5 mg group, and for the mean total daily beta-2 agonist use in the 10 mg group, in the modified ITT sample. For the FEV_1 measures, both doses of zafirlukast were superior to placebo. Mean change in FEV_1 percent predicted at endpoint (4-week) was 6.75 for the 5 mg group, 5.93 for the 10 mg group, and 3.08 for the placebo group. Mean change in absolute FEV_1 in liters at endpoint (4-week) was 0.14 for the 5 mg group, 0.10 for the 10 mg group, and 0.06 for the placebo group. However, zafirlukast treated groups tended to have more absenteeism from school for asthma, more physician contacts for asthma, and more withdrawals for asthma. The differences among the groups for these measures were small. Both doses of zafirlukast were well tolerated in this study population. Adverse events leading to withdrawals were overwhelmingly associated with asthma. Dose ordering for efficacy measures, and safety measures, including for laboratory measures of liver injury was not seen in this study. Overall, this study supports the safety and use of zafirlukast 5 mg and 10 mg doses in children 5 to 11 years of age with asthma.

Study 0139 was a four-arm, 1:1:1:1 randomized, multicenter, double-blind, placebo-controlled, dose-ranging, parallel-group study in patients 5 to 11 years of age with mild to moderate asthma (FEV_1 50-85% of predicted). The study design features, efficacy parameters, and limitations of efficacy assessment from a statistical point of view were similar to study 0079. One of the objectives of the study was to confirm the efficacy of 10 mg BID dose and assess whether higher doses of zafirlukast up to 40 mg BID would provide greater efficacy than the 5 and 10 mg BID doses. This study also included 4 periods: a 1-week screening period, a 7-14 day single-blind placebo run-in period, a 6-week double-blind period, and an optional 52-week open-label safety extension period. The double-blind treatment period was longer is this study than study 0079 (6 weeks vs 4 weeks). A total of 413 patients were randomized and 379 patients completed the study. During the double-blind period, patients were treated with placebo or zafirlukast (10 mg or 20 mg or 40 mg BID). In the open-label period, patients were treated with zafirlukast 20 mg BID. Given the limitations of statistical analyses, statistical significance was achieved for absolute FEV_1 in liters the 20 mg group, and AM and PM peak expiratory flow rate in the 10 mg group. For the spirometry measures, all three doses of zafirlukast showed a numerical superior response to placebo. Mean change in FEV_1 percent predicted at endpoint (6-week) was 6.52 for the 10 mg group, 7.93 for the 20 mg group, 7.69 for the 40 mg group, and 4.63 for the placebo group. Mean change in absolute FEV_1 in liters at endpoint (6-week) was 0.14 for the 10 mg group, 0.17 for the 20 mg group, 0.16 for the 40 mg group, and 0.09 for the placebo group. By most measures, zafirlukast 10 mg group showed greater evidence of effect. However, among the active treatment groups, the 10 mg group had the most beta-2 agonist use, absenteeism from school for asthma, and physician contacts for asthma. For most of these measures, the active treatment groups faired better than placebo. The numerical differences among the groups for these measures were small. All doses of zafirlukast were well tolerated in this study population. Adverse events leading to withdrawals were overwhelmingly associated with asthma. Dose ordering for efficacy measures, and safety measures, including for laboratory measures of liver injury was not seen in this study. Overall, this study

supports the safety and use of zafirlukast 10 mg dose in children to 11 years of age with asthma.

Efficacy assessment

Efficacy of zafirlukast is difficult to assess from the two pediatric studies alone. In fact, if these two studies were to be considered as stand alone, efficacy was not demonstrated convincingly for any of the doses. For many of the measures, 10 mg BID dose was as good as 5 mg BID dose, and dose ordering for the four doses (5, 10, 20, and 40 mg BID) was not seen for most of the efficacy measures. Improvement in FEV_1 was shown for zafirlukast, however, some other measures, such as absenteeism from school, physician contact for asthma, and beta-2 agonist use often went in the opposite direction, favoring placebo over active treatment. However, when the two pediatric studies are compared to the three adult studies that led to the approval of zariflukast in adults and adolescents 12 years of age and above, the picture is more favorable (Table 1).

Table 1. Comparison of efficacy measures* across the adult and pediatric studies for ITT population

	Adult studies†			Pediatric studies†	
	0029	**0057**	**0028**	**0079**	**0139**
FEV_1 in Liters	0.08 (507)	0.10 (92)	0.12 (41)	0.03 (103)	0.05 (100)
FEV_1 percent predicted	2.60 (506)	2.57 (92)	1.22 (41)	2.96 (103)	1.87 (100)
AM PEFR (L/min)	13.63 (504)	4.35 (94)	-8.92 (42)	-5.04 (103)	16.37 (95)
PM PEFR (L/min)	2.74 (502)	4.44 (91)	-12.76 (42)	-4.05 (102)	13.74 (93)
Asthma symptom score	-0.20 (506)	-0.14 (94)	-0.02 (43)	0.04 (103)	0.08 (95)
Number of nighttime awakenings	-0.47 (502)	-0.77 (95)	-0.76 (43)	0.25 (101)	0.16 (91)
Beta-2 agonist use (puffs per day)	-0.77 (504)	-1.11 (94)	-1.04 (43)	0.47 (103)	0.43 (95)

* Least-square mean difference between zafirlukast and placebo treated groups at endpoint. Results express as mean (number of patients).

† Results from 20 mg BID dose shown for adult studies, and for 10 mg BID dose shown for pediatric studies.

Source: NDA 20-547 medical officer review, and the pediatric efficacy supplement.

The sponsor submitted three pivotal efficacy studies in the original NDA (Table 1). Study 0029 was very large and therefore more "powerful" than studies 0057 and 0028. Study 0029 demonstrated that zafirlukast was statistically better than placebo for many efficacy measures, such as absolute FEV_1, FEV_1 percent predicted, AM peak expiratory flow rate, asthma symptom score, nighttime awakenings for asthma, and rescue beta-2 agonist use. Studies 0057 and 0028 demonstrated that zafirlukast was statistically better than placebo in reducing rescue beta-2 agonist use, but was statistically not better than placebo for any other efficacy measures. However, the effect sizes among the three adult studies were comparable, i.e., the magnitude of zafirlukast's efficacy over placebo was similar for most endpoints. This was some of the reasoning that led to the conclusion that zafirlukast was efficacious in treating asthma for patients 12 years of age and older. If one looks at the objective endpoints in the pediatric studies, such as the spirometry measures, the effect sizes are comparable to the adult studies (Table 1). FEV_1 percent predicted is perhaps the most reasonable spirometry measure in children because of their large size variability. Given that the pathophysiology of asthma is similar in adults and children, one can extrapolate these findings and conclude that zafirlukast is efficacious in the pediatric population. However,

the pediatric studies do not show dose-ordering, therefore, dose selection will need to made from the pharmacokinetic studies.

The pharmacokinetic data are reviewed in Dr. John Hunt's biopharmaceutics review. The sponsor submitted three pharmacokinetic studies, 0144, 0145, and 0152, with this NDA supplement, and cross-referenced study 0058 that was submitted for the original NDA. The biopharmaceutics reviewer has concluded that there is adequate data down to the age of 7 years that can be used for dose selection. Based on the pharmacokinetic studies, the projected systemic drug exposure in children 7 to 11 years of age using the proposed regimen of 10 mg BID would be approximately the same as that for adults using 20 mg BID. The pharmacokinetic data therefore support the approval of the 10 mg BID dose in children 7 to 11 years of age. The [redacted] dose proposed by the sponsor is expected to result in lower systemic drug exposure relative to the approved adult regimen. From a conservative perspective, and taking into account of variability and safety concerns, the proposed dose of [redacted] seems reasonable, however, there is no pharmacokinetic data to support approval of the [redacted] dose. Furthermore, there is no data to guide dose titration between the [redacted] and 10 mg BID doses.

Safety assessment

Zafirlukast was generally well tolerated in the clinical studies. A total of 811 patients were exposed to zafirlukast in the clinical studies. Of these, 788 patients were 5 to 11 years of age, and included 470 exposed for less than six months, 200 exposed for more than six months but less than one year, and 113 exposed for at least one year. The mean age of all patients was 8.7 years. Adverse events more frequently reported by patients taking zafirlukast than placebo and considered to be drug-related by the clinical investigators were headache, nausea, gastroenteritis, and epistaxis. Patients in the open-label extension studies reported headache and variety of upper and lower respiratory adverse events. Serious adverse events and withdrawals due to adverse events were mostly due to asthma exacerbation. There were no deaths in the studies. Clinical laboratory values showed small shifts to higher categorical values during zafirlukast treatment for AST and ALT, but only two values greater than 100 U/L were recorded and one of these occurred two months after treatment had ceased. Safety profile of zafirlukast in children was benign and similar to that seen in the adult program.

The post-marketing spontaneous adverse event reporting on zafirlukast is somewhat troubling due to reports of hepatic impairment of varying degrees and eosinophilic conditions including Churg-Strauss Syndrome. Since the launch of zafirlukast in US on November, 1996, there have been 105 cases of 133 adverse events involving the liver that includes 77 reports of liver function test abnormalities, 31 reports of hepatomegaly or hepatitis, 17 reports of icterus or hyperbilirubinemia, 8 reports of liver failure or cirrhosis, 1 death, and 1 liver transplantation. A 67-year-old female died of liver failure in Norway, and a 49-year-old female in US underwent liver transplantation due to liver failure. These post-marketing adverse events are detailed in Dr. Anthracite's review. The association between zafirlukast and liver injury is noted, however, the causality is not definitely established.

The signal of hepatic impairment in the pediatric studies is similar to that seen in the adult studies. There is no reason to believe that children will be more susceptible to liver injury by zafirlukast than adults. Also, the slight elevation of liver enzymes seen in the clinical studies was not convincingly dose related. Vasculitis and Chrug-Strauss Syndrome was not seen in any adult or in the pediatric clinical studies. These are rare and again not dose related. Therefore, the safety profile of zafirlukast in patients between the ages of [redacted] and 11 years is expected to be same as that in patients 12 years of age and above. Although these post-marketing adverse event reports would not preclude approval of zafirlukast in children, one would need to be cognizant of them.

Recommendation

This pediatric efficacy supplement as amended by the sponsor on September 14, 1999, is recommended for approval under the provisions of "pediatric use," 21 CFR 201.57(f)(9)(iv). The pathophysiology and course of asthma is similar in the adult and in the pediatric population. The sponsor has submitted two studies that show that the effects of zafirlukast, both beneficial and adverse, are similar in the pediatric and adult population. These permit extrapolation from the adult data to conclude that the drug is safe and effective for prophylaxis and chronic treatment of asthma in the pediatric population. The pharmacokinetic data support 10 mg BID dosage down to the age of 7 years. Specific labeling comments regarding the pediatric section of the package insert will be forwarded separately to the sponsor.

NDA 20-547/S-007

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

NOV 2 1999

Dear Mr. DeSiato:

We acknowledge the receipt of your October 18, 1999, submission containing final printed labeling in response to our September 17, 1999, letter approving your supplemental new drug application for Accolate (zafirlukast) Tablets, 10 and 20 mg.

We have reviewed the labeling that you have submitted in accordance with our September 17, 1999, letter, and we find it acceptable.

If you have any questions, contact Ms. Parinda Jani, Project Manager, at (301) 827-1064.

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL