CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 03/28-29/96

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SUMMARY MINUTES

Summary Minutes
for the
Pulmonary-Allergy Drugs Advisory Committee Meeting
March 28-29, 1996
Food and Drug Administration
Center for Drug Evaluation and Research
Quality Hotel, Maryland Ballroom
8727 Colesville Road, Silver Spring, Maryland

Members Present
Richard C. Ahrens, M.D. (Chairman)
Berri H. Mitchell, R.N., M.S.N.
Shirley Murphy, M.D.
Courtney Crim, M.D.
James Li, M.D., Ph.D
John Jenne, M.D

Consultants
Vernon Chinchilli, Ph.D
Carrol Cross, M.D.
Mark Liu, M.D.
Molly Lee Osborne, M.D., Ph.D.

Guest
James N. Barananiuk, M.D

Presenters for Zeneca Pharmaceuticals
John F. Weet
Catherine Bonuccelli, M.D.

Executive Secretary
Leander B. Madoo

FDA Participants
James Bilstad, M.D.
John K. Jenkins, M.D.
Robert Meyer, M.D.
Peter Honig, M.D.
Dale Conner, Pharm.D.
Raymond Anthracite, M.D.
Susan Johnson, Pharm.D.

Members Absent
Lynn Taussig, M.D.
Susan Pingleton, M.D.

Presenters for 3M Pharmaceuticals
Gene Colice, M.D.
James Elvecrog, M.S.
Chet Leach, Ph.D.

These summary minutes for the March 28-29, 1996 meeting of the Pulmonary-Allergy Drugs Advisory Committee were approved on 10/7/96.

I certify that I attended the March 28-29, 1996 meeting of the Pulmonary-Allergy Drugs Advisory Committee and that these minutes accurately reflect what transpired.

/S/
Leander B. Madoo
Executive Secretary

/S/
Richard C. Ahrens, M.D.
Chairman

The forty-second meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) was held March 28-29, 1996, at the Quality Hotel, Maryland Ballroom, 8727 Colesville Road, Silver Spring, Maryland. During the meeting, which was open to the public in its entirety, the committee reviewed and discussed two new drug applications (NDAs) and responded to questions posed by the agency based on the information presented. The topics were: (1) NDA 20-547, Zeneca Pharmaceuticals, Accolate (zafirlukast) Tablets. The proposed indication for Accolate is as an oral anti-inflammatory agent for use in the prophylaxis and chronic treatment of asthma and as a first-line maintenance therapy in patients with asthma who are not adequately controlled by PRN B2-agonist alone; and (2) NDA 20-503, 3M Pharmaceuticals, Epaq, an albuterol metered dose inhaler which is the first to utilize a hydrofluoroalkane propellent. The proposed indication is for treatment or prevention of bronchospasm in patients with reversible obstructive airway disease. The briefing material conveyed to the PADAC prior to the meeting included the following: (1) FDA developed questions relating to the NDA data, (2) summaries of the NDA data provided by each sponsor, and (3) FDA Briefing Document prepared by the Division of Pulmonary Drug Products, Center for Drug Evaluation and Research.

OPEN SESSION:

The Chairman, Dr. Richard Ahrens, opened the meeting at 8:30 a.m. Thursday, March 28, 1996, and welcomed the committee members and consultants. There were approximately 150 persons in the audience for the first day session. Mr. Leander B. Madoo, FDA, delivered a statement of conflict of interest and provided administrative announcements.

Conflict of Interest Statement

The conflict of interest statement noted that a full waiver was granted to Courtney Crim, M.D.; which allowed him full participation and voting on the questions relating to Accolate, NDA 20-547. In addition Mark Lui, M.D., was granted a limited waiver which permitted him to participate in the discussion on Accolate Tablets without voting. All other participants had no potential conflict of interest for this issue when evaluated against the agenda.

Open Public Hearing

There were no requests to speak during the Open Public Hearing, so Dr. Ahrens, PADAC Chairman, proceeded to the next topic on the Agenda - committee consideration of Accolate.

Sponsor Presentation: Zeneca Pharmaceuticals on Accolate (zafirlukast)

Dr. John F. Weet, Zeneca Pharmaceuticals, specified the proposed indication for Accolate as follows: (1) for use as a first-line maintenance therapy in patients with asthma who are not adequately controlled already by prn beta-agonists and (2) for use in the prophylaxis and chronic treatment of asthma. He explained that when leukotrienes bind to specific receptors in the lung bronchoconstriction, increased mucus secretion, and edema formation are observed and that Accolate, a leukotriene receptor antagonist, blocks receptor binding of leukotrienes and contributes to the blockade and the migration of the symptoms of asthma.

Dr. Catherine Bonuccelli, Zeneca Pharmaceuticals, reviewed the data primarily from four studies efficacy studies: one 6-week placebo-controlled dose-ranging 739 patient study and three U.S. double-blind, controlled , long-term (13 week) studies involving 1,723 subjects. Dr. Bonucelli explained that the lowest effective dose of accolate was determined to be 20 mg BID and that the Phase III trials used daytime asthma symptom score as the key criterion for patient selection and the efficacy endpoints for the Phase II trials were in order of priority: (1) symptoms (daytime and nighttime); B2-agonist use, and (3) pulmonary function. She noted that the Phase III studies enrolled patients with an FEV1 of at least 55% predicted with no upper cutoff.

Dr. Bonuccelli summarized the overall conclusions for the clinical efficacy and safety of Accolate as follows:

Efficacy Conclusions- (1) Accolate's onset of clinical efficacy is demonstrated with in one week of starting treatment and is sustained over 13 weeks; (2) the mean improvements in symptoms are a 26% decrease in daily symptoms, a 25% decrease in mornings with asthma, and a 22% decrease in nighttime awakenings; (3) both morning peak expiratory flow rates (PEFR) and 1-second forced expiratory volume (FEV1) improved more with Accolate treatment than with placebo; and Accolate decreased B2-agonist use and asthma exacerbations compared with placebo, indicating an improvement in control of asthma.

Safety Conclusions- (1)adverse event profile of Accolate is similar to that of placebo; (2) clinically relevant laboratory abnormalities are rare - although in the greater than 55-year old patient population, Accolate had a higher incidence of infection reported compared to placebo in five out of 20 protocols (majority of them were mild and resolved while on treatment); and (3) Accolate is safe at doses of greater than 40 mg/day supporting the use of the to-be-marketed tablet (20mg).

FDA Presentation on NDA 20-547 Accolate

Clinical Efficacy Review

Dr. Peter Honig, FDA Medical Officer, outlined the structure of FDA's presentation and provided efficacy conclusions on the clinical program data for Accolate. He focused his discussion on the three large U.S. efficacy trials of 12 weeks of active treatment or longer where the patients were mild to moderate in asthma severity and were $\geq$ 12 years of age (except trial 28). The efficacy assessments used in the trials consisted of diary card scoring by the patient and clinic visit - FEV1 obtained at each scheduled visit. Dr. Honig provided the following conclusions and concerns for his efficacy review of the data: (1) Accolate treatment results in a small but consistent effect which achieves statistical significance for most efficacy parameters in only the largest clinical trial; (2) Post hoc analyses, based on demographic or baseline disease severity parameters, do not allow characterization of potential 'responders' to Accolate; and (3) does the small but consistent mean treatment effect provide reassurance that Accolate provides clinically meaningful benefits as a first-line agent in this patient population?

Biopharmaceutics/ Pharmacokinetics Review

Dale Conner, FDA Pharmacokinetics Reviewer, presented the following observations on the NDA data: (1) Accolate is highly variable in systemic exposure from a given dose; (2) many factors (food, concurrent disease, drug interactions, age and time of day) contribute to the variability; and (3)this variability may make clinical response more unpredictable for individual patients. He noted that results from *in vitro* studies indicate that Accolate inhibits two cytochrome P450 group isoenzymes and possibly a third. These metabolism studies have not been confirmed *in vivo* yet; however, there is concern for inhibition or drug interactions for Accolate. Dr. Conner mentioned that the sponsor has initiated human drug interaction tests studying terfenadine.

Safety Summary

Dr. Raymond Anthracite, FDA Medical Officer, provided an overview of clinical safety and adverse effects for the NDA. He stated that Accolate has a relatively safe clinical profile. He noted that adverse events associated with the drug had a very small incidence

over placebo (e.g. G.I. symptomatology) and a small excess elevation of alanine aminotransferase (ALT) seen over placebo.

Overall Summary Conclusions

Dr. Peter Honiq summarized the agency's review of the drug, as follows: (1) Accolate has a small but consistent effect which achieves statistical significance versus placebo in the largest clinical trial; (2)using cromolyn as an active control (study 57) showed that cromolyn had a comparable, if not greater clinical effect than Accolate; and (3) Accolate appears to be safe and quite well tolerated - although long term safety beyond 12 weeks is still being studied.

Open Committee Discussion on the Agency proposed Questions for NDA 20-547 Accolate

Dr. Ahrens put the following questions to the committee:

Efficacy

The sponsor has submitted three U.S. double-blind, controlled, long-term (12 week) studies to support the efficacy of zarfirlukast in patients with mild to moderate asthma. One of these studies(Study #0028) was a dose-ranging trial investigating zafirlukast doses up to 80 mg bid. Another (Study #0057) included inhaled cromolyn (1600 ug QID) as an active control. The third and largest trial (Study # 0029) compared zafirlukast to placebo.

Question A. Has the efficacy of zafirlukast (Accolate) for the treatment of mild to moderate asthma been demonstrated?

Answer: The committee voted 7-2 in the affirmative. One of the negative voters stated that he agreed that statistical efficacy was shown but not clinical.

Question: If yes (clinical efficacy demonstrated), at what dose(s)?

Answer: The members voting in the affirmative agreed that the recommended dose should be 20 mg bid for zafirlukast.

Question: If no (clinical efficacy not demonstrated), what additional studies would be required?

Answer: Of the two dissenting panel members: one stated that studies where clinically significant changes in symptom scores (defined a prior) can be demonstrated; and the other commented that he would be interested in seeing results from anther multi-center trial done in more moderately severe asthmatics using zafirlukast.

Safety

Over 3000 subjects have been exposed to zarfirlukast of which 1723 were asthmatics participating in trials of at least 12 weeks duration. The to-be-marketed (TBM) formulation of zarfirlukast is more bioavailable than the formulations used in the clinical trials and results in higher exposures to the drug. Clinical trial data from exposures to 80 mg/day and higher may serve, in part, to support the safety of the 40 mg/day TBM formulation. The long-term safety database consists of 547 patients exposed to the clinical formulation of zafirlukast at 40 mg/day for at least 51 weeks.

Question A: Has the sponsor submitted a sufficient safety database to characterize adequately the frequency and severity of short-term (< 12 weeks) common adverse effects (e.g., changes in symptoms, vital signs, laboratory tests, and electrocardiograms) of the to-be-marketed formulation of zafirlukast at the proposed dose of 20 mg bid?

Answer: The committee voted 9-0 in the affirmative - agreeing that short-term common

adverse events had been adequately characterized in the NDA safety data dase.

Question B. Has the sponsor submitted a sufficient database to characterize adequately the long-term (> 12 weeks) common adverse effects (e.g., changes in symptoms, vital signs, laboratory tests, and electrocardiograms) of the to-be-marketed formulation of zafirlukast at the proposed dose of 20 mg bid?

Answer: Six (6) panel members voted affirmatively that long-term common adverse effects have been adequately characterized in the NDA safety data base, while three (3) voted negatively.

Question: If not, what additional studies and/or analyses would be required?

Answer: Dr. Ahrens noted that during the general discussion period that panel agreed that electrocardiogram data needs to be gathered.

Approvability

Question: Do you recommend that zafirlukast be approved as chronic maintenance therapy for patients aged 12 years or greater with mild to moderate asthma?

Answer: Initially, the committee was prepared to vote for approval of Accolate with the understanding that drug interaction studies would be conducted prior to approval. However, FDA Pulmonary Drug Product Division Director John Jenkins, MD, requested that the committee vote on the recommendation with that data encompassed by the NDA. The committee voted against recommending Accolate (zafirlukast) the vote was 6-3.

Question: If not, what additional studies would be required?

Answer: The committee agreed that zafirlukast should undergo additional drug interaction studies (with terfenadine, ketoconazole, and cimetidine) for mild to moderate asthma patients before being reconsidered for approval.

Phase 4 Commitments

Question: If zarfirlukast is recommended for approval, what, if any, post-marketing studies would you recommend be completed by the sponsor?

Answer: Several future studies were recommended by the committee, including looking at severe asthma, seasonal asthma, the elderly, children, food interactions, dose-ranging studies, and comparison trials with theophylline and inhaled steroids.

Pediatric Approval

FDA regulations (21 CFR 201.57) state that drugs for pediatric age groups may be approved based not only on studies in patients of the age range for which approval is sought, but also on adequate and well-controlled studies in adults together with other information supporting pediatric use may include, for example, pharmacokinetic data, pharmacodynamic data, and safety data.

Question: What studies would you recommend the sponsor conduct to support approval of zafirlukast in pediatric patients?

Answer: The committee voted 6-3, that prior to being approved, efficacy studies on Accolate be performed for pediatric patient population of 6-12 years of age.

Those in favor of an efficacy trial stated that on the basis of the data derived from adults it would be difficult to know how more or less effective the drug is in children and that pharmacokinetic data is needed children, as well.

NDA 20-503 Epaq (Albuterol Sulfate MDI)

Second day, Pulmonary-Allergy Drugs Advisory Committee Meeting

Issue: Epaq, 3M Pharmaceuticals' chlorofluorocarbon (CFC)-free albuterol metered-dose inhaler. Epaq uses hydrofluroalkane (HFA) 134a as a propellant rather than CFC. Indication sought: for the treatment and prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease. Prior to the meeting the committee received briefing material supplied by the Division of Pulmonary Drugs, FDA and from 3M Pharmaceuticals.

At 8:30 a.m. Friday March 29, 1996, Dr. Richard Ahrens reconvened the meeting. There were approximately 125 persons in the audience. Mr. Leander Madoo, Executive Secretary PADAC, delivered the conflict of interest statement.

Conflict of Interest Statement

The conflict of interest statement noted that full waivers have been granted to Berri Mitchell, R.N.; Richard Ahrens, M.D.; and Shirley Murphy, M.D.; which allowed them full participation and voting on the questions relating to Epaq, NDA 20-503. All other participants had no potential conflict of interest for this issue when evaluated against the agenda.

Introductory Remarks

Dr. John Jenkins, Division Director Pulmonary Drug Products - FDA, noted that Dr. Richard Ahrens term as PADAC Chairman would be expiring before the next committee meeting. He extended his sincere thanks to Dr. Ahrens for serving as Chair of the PADAC for the past three years. Dr. Ahrens expressed his appreciation for the opportunity to serve the committee and the Agency. With respect to the agenda topic Dr. Jenkins mentioned that the 3M product is the first CFC-Free Albuterol MDI to be reviewed by FDA. He provided some background to the 1992 Montreal Protocol under which signatories agreed to eliminate CFCs by January 1, 1996 (due to the suspected role of CFCs damaging the ozone layer of the upper atmosphere). Dr. Jenkins explained that CFC-containing MDIs currently are available under an essential use exemption and will have to be reformulated or be removed from the market when the waivers for essential use are no longer granted.

Open Public Hearing

Dr. Ahrens announced the Open Public Hearing portion of the meeting and invited two groups, which had previously requested participation, to address the committee. Speaking in turn were: the Stratospheric Protection Division, U.S. Environmental Protection Agency (EPA) represented by Mr. Clayton Frech and Friends of the Earth, Ozone Protection Campaign represented by Ms. Corinna Gilfillan. Both groups stated that they are highly supportive of industry and FDA collaborating in the development of CFC-free pharmaceuticals and that their introduction into the marketplace will be of benefit to the ozone layer and human health. There was one additional audience member who requested to speak a Mr. Allen Miller, Center for Global Change - University of Maryland, College Park, reiterated the

importance of CFC phaseout. There were no additional comments from the public during the Open Public Hearing. Dr. Ahrens proceeded to the next topic on the agenda - committee consideration of Epaq.

Open Session Agenda Topic: New Drug Application (NDA) 20-503, Epaq

Sponsor Presentation: 3M Pharmaceuticals

Dr. Gene Colice, 3M-Clinical Research, Outlined the structure of the Sponsor presentation. He noted that Epaq is currently approved for use in 22 countries around the world.

Dr. James Elvecrog, 3M Pharmaceuticals, summarized the nonclinical laboratory conclusions form the NDA, as follows: (1) Epaq has matched the in vitro performance characteristics of Ventolin, a currently marketed albuterol MDI (which uses a CFC propellant); (2) Epaq delivers the same amount of albuterol with the same particle distribution as marketed CFC product; and Epaq is equivalent to the marketed CFC product with respect to laboratory parameters related to drug delivery.

Dr. Chet Leach, 3M Pharmaceuticals, reviewed the preclinical testing program for Epaq and provided the following evaluations: (1) HFA-134a has an extremely low order of toxicity, there is no organ accumulation observed, nor mutagenic or carcinogenic activity found and (2) Epaq has a very similar safety profile to the CFC albuterol products.

Dr. Gene Colice, 3M Pharmaceuticals, discussed the results of the five primary studies in the clinical development program for Epaq. He noted that the primary efficacy variable in the clinical program was forced expiratory volume in 1 sec (FEV1)- specifically peak FEV1 effect, the duration of the FEV1 response, and the area under the curve; and that the patient population across the studies had chronic stable asthma Ages 18-65 years of age) whose FEV1 was between 40 and 80% of predicted. Dr. Colice stated that clinical studies have shown comparable bronchodilator efficacy and similar safety profiles for Epaq and CFC Albuterol with multiple doses over a short time period, for two puffs of each product, with repeated dosing over 12 weeks, with long term (1-year of dosing and with switch from the original product to the new product. The supporting studies have confirmed and extended these findings.

FDA Presentation on Epaq NDA 20-503

Dr. Susan Johnson, FDA Medical Reviewer, presented her review conclusions of the NDA data for Epaq, as follows: (1) the sponsor adequately demonstrated the efficacy of Epaq relative to placebo; (2) Epaq showed clinical comparability to ventolin in the populations studied (patients 12 years of age and older with reversible obstructive airway disease); and (3) Epaq demonstrated an acceptable safety profile.

Open Committee Discussion on the Agency proposed Questions for NDA 20-503 Epaq (Albuterol Sulfate MDI)

Dr. Ahrens put the following questions to the committee:

Efficacy

The sponsor submitted two randomized, double-blind, placebo-controlled trials to demonstrate the effectiveness of Epaq in the treatment and prevention of bronchospasm in patients with reversible obstructive airway disease, Trials 1031 and 1012.

1. Have these trails adequately demonstrated the efficacy of Epaq at the proposed dose?

Answer: The committee vote was 9-0 in the affirmative

2. Dose the NDA efficacy database support comparable efficacy for the proposed dose of Epaq relative to the approved dose of Ventolin Inhalation Aerosol *in the population studied*?

Answer: The committee vote was 9-0 in the affirmative

Safety

In the NDA database the sponsor has presented safety data from 393 asthma patients who were exposed to Epaq for up to three months. The database also contains data from 289 asthma patients who were exposed to Epaq for six months and 105 asthma patients who were exposed to Epaq for one year or more.

1. Has the sponsor submitted sufficient evidence to support the safe use of Epaq as chronic therapy for the treatment of reversible obstructive airway disease in adults?

Answer: The committee vote was 9-0 in the affirmative

2. Does the NDA safety database support comparable safety for the proposed dose of Epaq relative to the approved dose of Ventolin Inhalation Aerosol in the population studied?

Answer: The committee vote was 9-0 in the affirmative

Approvability

Do you recommend that Epaq be approved for the treatment and prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease?

Answer: The committee vote was 8 affirmative and, and one abstention

a. If yes, what, if any, post-marketing studies would you recommend be conducted with 8 Epaq in patients with reversible obstructive airway disease?

Dr. Ahrens recommended that a proper study establishing the relative potency of the Epaq MDI be done as an essential part of a Phase IV study. In earlier committee discussion, Dr. Ahrens had commented that the NDA dose-ranging study did not show a significant dose-response relationship and relative potency information is lacking. Another committee member recommended a Phase IV study be performed with a commonly used holding chamber to determine whether Ventolin and Epaq are equivalent when used with the spacer.

Dr. Ahrens thanked the agency, sponsor, and committee for their participation in the meeting. The meeting was adjourned at 2:45 p.m.