

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20750

ADMINISTRATIVE DOCUMENTS

Clinical Team Leader Memorandum - Addendum

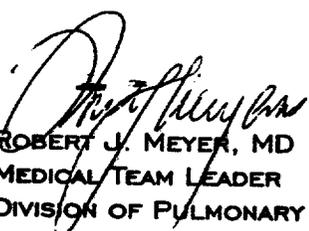
Memorandum to: NDA 20-750 file
Product: Tilade Solution for nebulization
Memo date: 9-30-97
Memo from: Robert J. Meyer, MD Medical Team Leader, DPDP

TO COMPLETE THE FILE ON THIS NDA, THIS MEMO IS BEING WRITTEN TO CLARIFY THE REVIEW OF THE 120 DAY SAFETY UPDATE, SINCE IT WAS REVIEWED BUT NOT SPECIFICALLY DETAILED IN THE MEDICAL OFFICER'S REVIEW DOCUMENT.

THE 120 SAFETY UPDATE WAS SUBMITTED BY RPR ON 2-6-97 WITH A CDER STAMP DATE OF 2-7-97. THE ENTIRE UPDATE CONSISTED OF 2 VOLUMES WHICH DETAILED THE RESULTS OF NON-US STUDY, CR2407, A FRENCH TRIAL OF NEDOCROMIL SODIUM INHALATION SOLUTION (4 ML TID) IN INFANTS. THIS WAS A SMALL STUDY, WITH 61 RANDOMIZED "INFANTS," AGES 6 MONTHS TO 3 YEARS. THIS STUDY CONTRIBUTES LITTLE TO THE SAFETY DATABASE DUE TO THE LIMITED NUMBER OF CHILDREN IN THE STUDY, THE DIFFERENT DOSAGE EXAMINED AND THE POPULATION WHICH ONLY PARTLY INCLUDES THE LABELED POPULATION. WITH THE LIMITED DATA REPORTED IN THE 120 SAFETY UPDATE AND WITH DUE TO THE NATURE OF THOSE DATA, THEY WERE NOT INTEGRATED INTO THE ENTIRE SAFETY DATABASE.

THESE DATA DID NOT PROVIDE ANY INDICATION OF NEWLY OBSERVED ADVERSE EVENTS, NOR OF OCCURRENCES OF ADVERSE EVENTS OUT OF PROPORTION WITH THOSE PREVIOUSLY REPORTED. THERE WAS ONE CHILD WHO SUFFERED A SERIOUS BOUT OF RESPIRATORY FAILURE WHILE ON NEDOCROMIL (AS DETAILED IN A TRANSLATED CRF). HOWEVER, THIS CHILD APPEARED TO HAVE WHOOPING COUGH AND DID RECOVER WITHIN 3 DAYS FROM THIS SEVERE EPISODE. OTHERWISE, THE OCCURRENCE OF ADVERSE EVENTS IN THE TILADE-TREATED PATIENTS IS QUALITATIVELY AND QUANTITATIVELY SIMILAR TO THOSE IN THE VEHICLE-TREATED SUBJECTS.

THE OVERALL SAFETY DISCUSSION FROM THE MEDICAL OFFICER REVIEW SUFFICES IN SUMMARIZING THE SAFETY ASPECTS OF THIS PRODUCT.


ROBERT J. MEYER, MD 9/30/97
MEDICAL TEAM LEADER
DIVISION OF PULMONARY DRUG PRODUCTS

CC: Otulana/Medical Officer/HFD-570
Meyer/Medical Team Leader/HFD-570
Gallauresi/project manager/HFD-570
Division File/HFD-570
NDA #20-750

SEP 19 1997

Clinical Team Leader Review Memorandum

Memorandum to: NDA 20-750 file
Product: Tilade Solution for nebulization
Memo date: 9-17-97
Memo from: Robert J. Meyer, MD Medical Team Leader, DPDP

THIS MEMORANDUM IS TO DOCUMENT THE SECONDARY REVIEW CONCLUSIONS ON TILADE NEBULIZATION SOLUTION NDA, APPLICATION NUMBER 20-750. THE SECONDARY REVIEW WAS CARRIED OUT BOTH CONCURRENTLY WITH AND SUBSEQUENT TO DR. OTULANA'S PRIMARY CLINICAL REVIEW AND MS. BONO'S STATISTICAL REVIEW. THIS MEMORANDUM WILL HIGHLIGHT SOME OF THE EFFICACY AND SAFETY REVIEW ISSUES THAT FORM THE BASIS OF THE RECOMMENDATION FOR CLINICAL APPROVABILITY.

OVERVIEW:

NEDOCROMIL SODIUM AS A MOLECULAR ENTITY WAS APPROVED IN 1992 IN A METERED-DOSE FORMULATION - TILADE INHALER - FOR THE MAINTENANCE TREATMENT OF MILD-TO-MODERATE ASTHMA IN PATIENTS 12 AND ABOVE (WITH THE PEDIATRIC INDICATION DOWN TO AGE 6 BEING APPROVED FOR THE MDI WITHIN PAST YEAR). THE CURRENT NDA IS FOR A UNIT DOSE, LDPE-PACKAGED 0.5% SOLUTION OF NEDOCROMIL SODIUM FOR NEBULIZATION. THE APPLICATION CONTAINS A LARGE NUMBER OF TRIALS WHICH ARE MEANT TO ADDRESS BOTH ADULT AND PEDIATRIC INDICATIONS (AGES 2 AND ABOVE), AS WELL FOR USE IN A SETTING OF ON-GOING SYMPTOMATIC ASTHMA (E.G., AS A CONTROLLER) AND FOR USE IN MAINTAINING SYMPTOM-FREE PATIENTS (E.G., AS A PREVENTER), AND FINALLY WITH BOTH TID AND QID DOSING SCHEDULES.

EFFICACY:

THE TRIALS SUBMITTED FOR THIS PRODUCT ARE NOT UNIFORMLY FAVORABLE ON EFFICACY. THIS APPEARS TO BE DUE IN SOME INSTANCES TO THE CHOICE OF PRIMARY ENDPOINTS AND/OR TIME FRAME FOR ASSESSMENT. HOWEVER, IN OTHER CASES, THE TRIALS SIMPLY FAIL TO SHOW EVEN A TREND TOWARDS EFFICACY. OVERALL, THE SPONSOR DOES PROVIDE SUFFICIENT WITH THE DATA SUBMITTED FOR THERE TO BE A CONCLUSION OF EFFICACY FOR TILADE NEBULIZING SOLUTION IN COMPARISON TO PLACEBO, WITH CLEAR-CUT STATISTICAL SIGNIFICANCE ON THE *A PRIORI* DESIGNATED ENDPOINTS COMING FROM MULTIPLE STUDIES. THIS INCLUDES STUDY CR1408 (SYMPTOM REDUCTION STUDY, QID DOSING IN 13 - 70 YEAR OLD SUBJECTS); CR1574 (SYMPTOM REDUCTION, QID DOSING IN SUBJECTS AGES 6 - 12); AND STUDY CR2233 (SYMPTOM PREVENTION STUDY, WITH TID DOSING IN SUBJECTS 2 - 5 YEARS OF AGE). STUDIES THAT MIGHT HAVE SUPPORTED EFFICACY, BUT APPEARED TO FAIL DUE TO THE *A PRIORI* CHOICE ON ENDPOINTS/TIME PERIOD WERE CR2333 (SYMPTOM REDUCTION, QID DOSING AND 12 - 81 AGE RANGE) AND STUDY CR1978 (SYMPTOM PREVENTION, TID DOSING AND 6 - 12 AGE RANGE). IN ALL THESE STUDIES, THE STATISTICALLY SIGNIFICANT FINDINGS WERE FOR A MODEST EFFECT DEMONSTRATED ON SYMPTOMS, WITH A VARIABLE DEGREE OF SUPPORTIVE DATA COMING FROM AIR-FLOW ASSESSMENTS (PEFR AND/OR FEV₁), BRONCHODILATOR USE, AND OTHER MEASURES OF ASTHMA CONTROL. IT SHOULD BE NOTED THAT THE OVERALL DROP-OUTS DUE TO ASTHMA-RELATED ADVERSE EVENTS AND/OR LACK-OF-EFFICACY FAVORS TILADE OVER PLACEBO. ALTHOUGH THESE DATA WERE NOT INTENDED BY THE SPONSOR AS AN ENDPOINT, IT IS REASSURING THAT WHEN ALL THE US PIVOTAL TRIALS ARE CONSIDERED, TILADE TREATMENT APPEARS TO RESULT IN FEWER SIGNIFICANT ASTHMA-RELATED EVENTS THAN PLACEBO.

SAFETY:

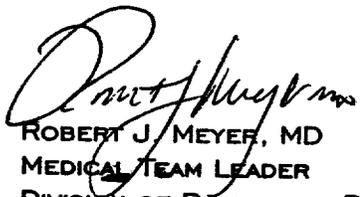
THE SAFETY DATA IN THIS NDA WERE REASONABLY EXTENSIVE, WITH 936 EXPOSED PATIENTS IN CLINICAL TRIALS, INCLUDING 523 SUBJECTS BELOW THE AGE OF 12. THESE DATA ATTEST TO THE SAFETY AND TOLERABILITY OF THIS FORMULATION IN MILD-TO-MODERATE ASTHMATICS. IT IS NOTABLE THAT THE INCIDENCE OF COUGH, BRONCHOSPASM AND DYSPNEA WERE ALL HIGHER IN VEHICLE CONTROL THAN IN TILADE SUBJECTS, SUPPORTING THE TOLERABILITY OF NEDOCROMIL IN THIS FORMULATION. THE MOST CONSISTENT DRUG-RELATED ADVERSE EVENT APPEARS TO TASTE PERVERSION/BAD TASTE. OVERALL, THE DATA IN THIS NDA STRONGLY INDICATE THIS PRODUCT TO BE SAFE FOR ITS INTENDED USE.

OVERALL CONCLUSIONS:

I AM IN AGREEMENT WITH DR. OTULANA'S ASSESSMENT THAT THIS APPLICATION IS APPROVABLE FROM THE CLINICAL STANDPOINT. I THINK AN INDICATION REFLECTIVE OF BOTH ITS USE AS A ASTHMA CONTROLLER AND SYMPTOM PREVENTER IN MILD-TO-MODERATE ASTHMATICS IS APPROPRIATE, WITH DOSING ROUTINELY BEING ON A QID SCHEDULE WITH TID TITRATION ALLOWED FOR STABLE SUBJECTS (WITH THE EXCEPTION OF A TID STARTING DOSE REGIMEN BEING APPROPRIATE TO RECOMMEND FOR THE SYMPTOM PREVENTION USE IN CHILDREN AGES 2 - 5). ALTHOUGH THE EFFICACY RESULTS SUGGEST A RELATIVELY MODEST EFFECT OF THIS PRODUCT, GIVEN THE VERY FAVORABLE SAFETY PROFILE AND THE NEED TO HAVE ALTERNATIVES TO CORTICOSTEROID THERAPY, PARTICULARLY FOR CHILDREN, I THINK THIS PRODUCT SHOULD BE APPROVED FOR THE U.S. MARKET.

RECOMMENDATION:

I RECOMMEND APPROVAL OF THIS PRODUCT, ONCE ALL CMC ISSUES AND LABELING ISSUES ARE RESOLVED. I DO NOT SEE ANY PHASE 4 COMMITMENTS BEING NECESSARY FROM THE CLINICAL STANDPOINT.

 9/18/97
ROBERT J MEYER, MD
MEDICAL TEAM LEADER
DIVISION OF PULMONARY DRUG PRODUCTS

CC: Otulana/Medical Officer/HFD-570
Meyer/Medical Team Leader/HFD-570
Gallauresi/project manager/HFD-570
Division File/HFD-570
NDA #20-750



RHÔNE-POULENC RORER PHARMACEUTICALS INC.

500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

**New Drug Application #20-750
Form FDA 356h
Item 13**

**Tilade® Nebulizer Solution
(nedocromil sodium inhalation solution)**

Item 13: Patent Information

Patent Information for the Tilade ® Nebulizer Solution (nedocromil sodium inhalation solution) original New Drug Application is found on the following pages.

APPEARS THIS WAY

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Item 13. Patent Information

- 1) Patent number 4,328,341
- 2) Date of expiration December 2, 2000
- 3) Type of patent Method of Manufacture
- 4) Name of patent owner Fisons Limited
- 5) U.S. representative Rhône-Poulenc Rorer Pharmaceuticals Inc.

The undersigned declares that Patent No. 4,328,341 covers the method of making Applicant's Tilade® nebulizer solution (nedocromil sodium) product. This product is currently approved under section 505 of the Federal Food, Drug and Cosmetic Act.

Signed:
Name:
Title:



Ross J. Oehler
Assistant General Counsel
Patents and Trademarks
Rhône-Poulenc Rorer Pharmaceuticals Inc.

Date: 8/6/96

APPROVED THIS WAY

APPROVED THIS WAY

Item 13. Patent Information

- 1) Patent number 4,474,787
- 2) Date of expiration October 2, 2001
- 3) Type of patent Drug Composition, Drug Product, Method of Use
- 4) Name of patent owner Fisons Limited
- 5) U.S. representative Rhône-Poulenc Rorer Pharmaceuticals Inc.

The undersigned declares that Patent No. 4,474,787 covers the formulation, composition, and method of use of Applicant's Tilade® nebulizer solution (nedocromil sodium) product. This product is currently approved under section 505 of the Federal Food, Drug and Cosmetic Act.

Signed:
Name:
Title:


Ross J. Oehler
Assistant General Counsel
Patents and Trademarks
Rhône-Poulenc Rorer Pharmaceuticals Inc.

Date: 8/6/96

SEE THIS WAY
ON ORIGINAL

SEE THIS WAY
ON ORIGINAL

Item 13 -Patent/Exclusivity Information

- 1) **Active Ingredient(s):** nedocromil sodium
- 2) **Strength(s):** 0.5% w/v in water/2.2 ml per ampule
- 3) **Trademark:** Tilade®
- 4) **Dosage Form (Route of Administration):** nebulizer solution
- 5) **Application Firm Name:** Rhône-Poulenc Rorer Pharmaceuticals Inc.
- 6) **IND Number:**
- 7) **NDA Number:** 20-750
- 8) **Approval Date:**
- 9) **Exclusivity – date first ANDA could be submitted or approved and length of exclusivity period:** Pursuant to Section 505(j)(4)(D)(iii) and 505(c)(3)(D)(iii) of the Federal Food, Drug and Cosmetic Act, no ANDA may be approved with an effective date which is prior to 3 years after the date of approval of this application.
- 10) **Applicable patent numbers and expiration date of each:**

US4,328,341	12/2/2000
US4,474,787	10/2/2001
- 11) **To the best of our knowledge, each of the clinical investigations included in this application meets the definition of "new clinical investigation" set forth in 21 CFR 314.108(a).**

A list of all published studies or publicly available reports of clinical investigations known to the applicant through a literature search that are relevant to the conditions for which we are seeking approval is attached. We have thoroughly searched the scientific literature and, to the best of our knowledge, the list is complete and accurate and, in our opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of the conditions for which we are seeking approval without reference to the new clinical investigation(s) in the application. The reasons that these studies or reports are insufficient are presented in the attachment as well.

EXCLUSIVITY SUMMARY for NDA # 20-750 SUPPL # —

Trade Name Tilade Neb. Sol. Generic Name Nedocromil

Applicant Name Rhône-Paulène Rorer HFD-570

Approval Date, if known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA? YES // NO /___/

b) Is it an effectiveness supplement? YES /___/ NO //

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES // NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES // NO //

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 yrs

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx-to-OTC switches should be answered NO-please indicate as such.)

YES // NO // OTC Switch //

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES // NO //

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES // NO //

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 19-660 Tilade MDT
NDA# _____
NDA# _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____
NDA# _____
NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

YES / / NO / /

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / / NO / /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / / NO / /

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / / NO / /

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

CR 1574, CR 2233, CR 2333

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES / / NO / /

Investigation #2, 3, 4 YES / / NO / /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES / / NO / /

Investigation #2, 3, 4 YES / / NO / /

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	<u>1574</u>	:	
IND #	YES <input checked="" type="checkbox"/>	:	NO <input type="checkbox"/> Explain: _____
		:	_____
Investigation #2	<u>2233</u>	:	
IND #	YES <input checked="" type="checkbox"/>	:	NO <input type="checkbox"/> Explain: _____
		:	_____
Investigation #3	<u>2333</u>	:	
IND #	YES <input checked="" type="checkbox"/>	:	NO <input type="checkbox"/> Explain: _____
		:	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	:	
YES <input type="checkbox"/> Explain _____	:	NO <input type="checkbox"/> Explain _____
_____	:	_____
_____	:	_____
Investigation #2	:	
YES <input type="checkbox"/> Explain _____	:	NO <input type="checkbox"/> Explain _____
_____	:	_____
_____	:	_____

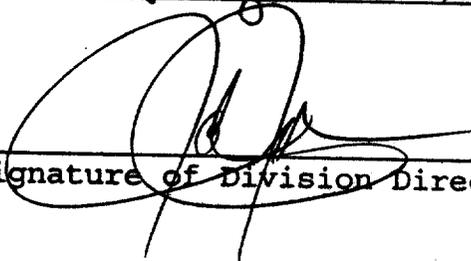
(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / / NO / /

If yes, explain: _____

Beverly Gallucci
Signature
Title: Project Manager

9/19/97.
Date


Signature of Division Director

10/1/97
Date

cc: Original NDA

Division File

HFD-93 Mary Ann Holovac

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # ~~100~~-750

Trade (generic) names Tilade Nebulizer Solution
(nedocromil sodium inhalation solution)

Check any of the following that apply and explain, as necessary, on the next page:

1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.
2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&NC studies in children.
- a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.
- b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)
3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).
- a. The applicant has committed to doing such studies as will be required.
- (1) Studies are ongoing.
- (2) Protocols have been submitted and approved.
- (3) Protocols have been submitted and are under review.
- (4) If no protocol has been submitted, on the next page explain the status of discussions.
- b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

✓ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

*This product is indicated for use in children
down to the age of 2 years. No further studies
are being conducted for less than 2 years of age.*

B. J. ... P.M.
Signature of Preparer

9/30/97
Date

cc: Orig NDA
HFD- /Div File
NDA Action Package

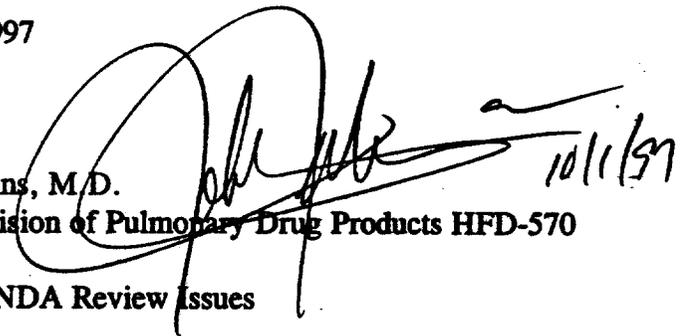
MEMORANDUM

DATE: October 1, 1997

TO: NDA 20-750

FROM: John K. Jenkins, M.D.
Director, Division of Pulmonary Drug Products HFD-570

SUBJECT: Overview of NDA Review Issues



Administrative

NDA 20-750 for Tilade Nebulizer Solution (nedocromil sodium inhalation solution) was originally submitted by Rhone-Poulenc Rorer on October 1, 1996. The current user fee goal date for NDA 20-750 is October 1, 1997.

Clinical

The proposed indication for Tilade Nebulizer Solution is for maintenance therapy in the management of mild-to-moderate asthma in patients two years of age and older. Nedocromil sodium is currently approved in the US in a CFC-based metered-dose inhaler and the indication was recently extended down to the age of 6 years for the maintenance therapy of asthma. In support of the proposed indication for Tilade Nebulizer Solution, the sponsor submitted a total of 8 adequate and well-controlled trials in patients with mild-to-moderate asthma 2 years of age and older. The trials evaluated the safety and efficacy of Tilade Nebulizer Solution in a treatment setting (i.e., in patients with symptomatic asthma) and in a prophylaxis setting (i.e., in patients with minimal asthma symptoms at baseline, but a history of seasonal exacerbations). For a more detailed analysis of the clinical program, please refer to the review prepared by Dr. Otulana and the Team Leader Memorandum prepared by Dr. Meyer. Three of the 8 trials submitted by the sponsor demonstrated the efficacy of Tilade Nebulizer Solution as judged by statistically significant improvements in asthma symptoms and PEFR compared to placebo-treated patients. In general, the other 5 trials also demonstrated some numerical advantage for Tilade Nebulizer Solution over placebo, however, consistent statistical significance was not achieved in the studies. The three positive studies included one in symptomatic asthmatics 12 years of age and older, one in symptomatic asthmatics 6 to 12 years of age, and one in relatively asymptomatic asthmatics 2 to 5 years of age with a history of seasonal exacerbations. Given that: 1) nedocromil sodium has previously been determined by the agency to be safe and effective for the maintenance treatment of asthma in patients 6 years of age and older (Tilade Inhalation Aerosol), 2) the sponsor has positive studies in each of the age ranges requested in the proposed labeling, and 3) the study in the new age range of 2-5 years was positive; I concur with Drs. Otulana and Meyer that the efficacy of Tilade Nebulizer Solution has been adequately established.

From a safety perspective, Tilade Nebulizer Solution was generally well tolerated with an adverse event profile very similar to vehicle placebo. The only consistent adverse reaction to

Tilade Nebulizer Solution was bad taste; nedocromil sodium is well recognized as an active ingredient that has an unpleasant taste. These bad taste complaints were not associated with more significant adverse reactions such as bronchospasm, etc.

From a labeling perspective, the one contentious issue with the sponsor has been the inclusion of the specific nebulizer systems used in the pivotal clinical trials in the labeling. The Division has adopted the position that the specific nebulizer system used in the pivotal clinical trials which serve as the basis for demonstrating the safety and efficacy of the product should be listed in the labeling. In addition, if the sponsor is able to link other nebulizer systems to the use of the product through appropriate bridging clinical trial to support their use as being safe and effective, other nebulizer systems can also be added to the labeling. Since only three of the eight pivotal trials submitted by the sponsor are considered as positive demonstrations of efficacy by the Division, only the nebulizer systems used in these three trials will be listed in the labeling. A statement will be included in the labeling that the safety and efficacy of Tilade Nebulizer Solution when used with other nebulizer systems have not been adequately established. This approach is consistent with the approach the Division recommended to CBER with the approval of Pulmozyme (rhDNase) and has recommended to other Divisions within CDER when consulted on this issue.

There are no outstanding clinical issues and the NDA is approvable from a clinical perspective with labeling as reflected in the marked-up final draft labeling which will be attached to the approval letter as terms of the approval.

Preclinical

Please refer to the pharmacology/toxicology review completed by Dr. Vogel and the Team Leader memorandum completed by Dr. Sun for complete details of the preclinical studies submitted in support of this application. As noted by Dr. Sun, the toxicity profile of nedocromil in chronic toxicity studies was minimal, with toxicity primarily localized to the GI tract. Nedocromil was not genotoxic or teratogenic and did not impair fertility in rats and rabbits. With regard to the carcinogenicity studies, nedocromil was negative for tumor formation in long-term studies in rats and mice, however, the dose levels used in the mouse may not have been sufficiently high to fully evaluate the carcinogenic potential in this species. The pharmacology reviewers recommend, and I concur, that there are adequate animal data to establish the safety of nedocromil sodium for chronic administration in humans (i.e., negative genotoxicity studies, negative two-year study in rats with a safety margin of approximately 60 fold based on serum AUC, negative 21-month study in mice with a safety margin of 6 fold based on serum AUC, and the overall benign toxicity profile observed for the drug in other studies such as reproductive toxicity).

There are no outstanding issues and the NDA is approvable from a preclinical perspective with labeling as reflected in the marked-up final draft labeling which will be attached to the approval letter as terms of the approval.

CMC -

Tilade Nebulizer Solution is supplied in unit-dose LDPE ampules at a concentration of 0.5%. Each ampule contains 11 mg of nedocromil sodium. For complete details of the CMC data submitted to this application, please see the review prepared by Dr. Kim. The sponsor has made a Phase 4 CMC commitment to set a specification and test for color determination of the solution within 6 months of the date of approval. Such data will be submitted as a supplement. The sponsor will be reminded of this commitment in the approval letter. The sponsor has also committed to implement an electronic leak detection system to assess container integrity. Dr. Cooney, microbiology Team Leader, believes that the current procedures in place by the sponsor are adequate to assure sterility of the product and that the validation data for the new electronic leak test are not required prior to approval of the NDA.

There are no outstanding CMC issues and the NDA is approvable from a CMC perspective with labeling as reflected in the marked-up final draft labeling as submitted by the sponsor which will be appended to the approval letter as terms of the approval. The sponsor will be reminded of their Phase 4 CMC commitments and their other agreements in the approval letter.

Clinical Pharmacology and Biopharmaceutics

Plasma concentrations of nedocromil sodium following inhalation are inadequate to allow completion of formal pharmacokinetic analyses. For further details, please refer to the review completed by Dr. Chen.

There are no outstanding clinical pharmacology and biopharmaceutics issues and the application is approvable with labeling as reflected in the marked-up final draft labeling which will be attached to the approval letter as condition of the approval.

Data Verification

The Division of Scientific Investigations (DSI) was not consulted to conduct audits of clinical trial sites for this application due to the fact that nedocromil sodium by inhalation has been previously demonstrated to be safe and effective when administered by inhalation and due to the fact that many of the investigators involved in the conduct of the pivotal clinical trials for this NDA have been audited recently for their conduct of clinical trials under other NDAs and found to be acceptable. Based on limited auditing of data conducted by Dr. Otulana, there are no concerns that would call into question the overall integrity of the NDA database.

Labeling

The proposed trade name, Tilade Nebulizer Solution, is acceptable to the Division, provided the established name is listed as "nedocromil sodium inhalation solution". The final draft package insert, patient instructions for use, and container and carton labeling submitted by the sponsor have been reviewed by the appropriate disciplines and are acceptable with a few minor changes which will be indicated in the marked-up labeling which will be attached to the approval letter as a condition of the approval.

Conclusion

There are no outstanding issues from any discipline with regard to this application and the

application can be APPROVED with labeling that is identical to the marked-up final draft labeling which will be included with the approval letter as a condition of the approval. The sponsor will be reminded in the approval letter of their Phase 4 CMC commitments.

cc: -
NDA 20-750
HFD-570 Division Files
HFD-570/Jenkins
HFD-570/Schumaker
HFD-570/Gallauresi
HFD-570/Meyer

APPEARS THIS WAY
ON ORIGINAL

SEP 27 1997

INTEROFFICE MEMO

TO: NDA 20750
FROM: C. Joseph Sun, Ph. D.
SUBJECT: Team Leader NDA Review Memo
DATE: September 27, 1997

C. Joseph Sun Sept. 27, 1997

I concur with the pharmacologist's conclusion that the pharmacology and toxicology of Tilade (Nedrocromil sodium) Inhalation Solution have been adequately studied and that the drug is approvable from a preclinical standpoint.

Nedrocromil inhibited a variety of cellular inflammatory processes that may contribute to allergic asthma. In vitro studies on human or monkeys bronchoalveolar cells, it inhibited the release of mediators. Nedrocromil reduced antigen-induced airway microvascular leakage in guinea pig and PAF-induced bronchoconstriction in allergic sheep.

Toxicity studies were performed in rats (one month by i.v., 2 months by subcutaneous and up to 6 months by inhalation) and dogs (up to 12 months by inhalation and subcutaneous). The data showed that it has a relatively low order of toxicity and major organ of effect was gastrointestinal tract (loose feces, diarrhea, salivation and emesis).

Nedrocromil sodium did not impair the fertility nor caused any teratogenic effects in rats and rabbits.

Nedrocromil sodium was not genotoxic in the Amest test, mitogenic gene conversation assay in *Saccharomyces cerevisiae*, mouse lymphoma assay, chromosome aberration assay in human lymphocytes and in vivo micronucleus test.

Carcinogenicity studies were conducted in mice (21 months by dietary) and rats (24 months by inhalation). The doses tested in mice may not have been sufficiently high to fully evaluate the carcinogenic potential in this species. No tumors were found in both studies.

With regard to labeling, carcinogenesis, mutagenesis and impairment of fertility and pregnancy category B sections on the package insert have been revised to incorporate the above-mentioned preclinical findings.

There is no outstanding preclinical issue.

Orig. NDA
HFD-570/Division file
HFD-570/Sun
HFD-570/Vogel
HFD-570/Gallauresi