CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-082

~~ADMINISTRATIVE DOCUMENTS~~

CORRESPONDENCE

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: HFD-400/OPDRA/Assoc. Director for Medication Error Prevention			FROM: HFD-570/DPADP/Hilfiker	
DATE: February 4, 2000	IND NO.:	NDA NO.: 21-082	TYPE OF DOCUMENT: Original submission	DATE OF DOCUMENT: October 7, 1999
NAME OF DRUG: Tavist Allergy/Sinus/Headache	PRIORITY CONSIDERATION: standard		CLASSIFICATION OF DRUG: 5S	DESIRED COMPLETION DATE: June 1, 2000
NAME OF FIRM: Novartis Consumer Health				

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ■ OTHER *(SPECIFY BELOW)*: Tradename Consult

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER:	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: This is a direct-to-OTC NDA application. Evaluation of the tradename should be based partially on prevention of consumer medication errors.

cc: Original NDA 21-082
HFD-570/~~Div. Files~~
HFD-570/Hilfiker, Lee, Khorshidi
HFD-560/Parmelee

SIGNATURE OF REQUESTER: /S/	METHOD OF DELIVERY (Check one): ■ MAIL ☐ HAND
SIGNATURE OF RECEIVER: /S/ 2-4-00	SIGNATURE OF DELIVERER:

C:\my_documents\N21082\00-02-04.namecon.doc

ORIGINAL

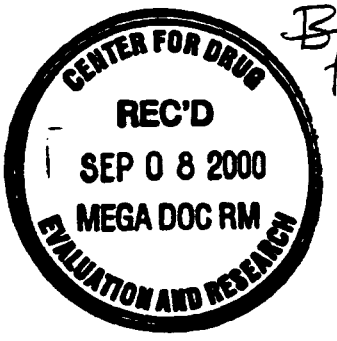
Nico C. Nicolaou
Manager, Regulatory Affairs

Novartis Consumer Health, Inc.
560 Morris Avenue
Summit, NJ 07901-1312

Tel 908 598 7600
Fax 908 273 2869

NOVARTIS

ORIG AMENDMENT



September 7, 2000

Robert J. Meyer, M.D., Director
Division of Pulmonary Drug Products, HFD-570
Document Control Room 10B03
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Tavist NDA 21-082 - Response to FDA Approvable Letter of August 4, 2000

Dear Dr. Meyer:

Reference is made to Tavist® Allergy/Sinus/Headache NDA 21-082 (Clemastine fumarate / Pseudoephedrine hydrochloride/Acetaminophen) Tablets submitted to FDA on October 7, 1999. Further reference is made to your approvable letter of August 4, 2000 for the above mentioned NDA.

Included in this submission is a point by point response to each of the questions from your August 4, 2000 letter, including revised 'draft' labeling of the carton and blister (foil).

Finally, as acknowledged in a September 5, 2000 telephone call from Mr. David Hilfiker of your division, the agency confirmed that a safety update for this resubmission is not required due to the length of time from the original submission and the nature of the use of the subject product.

We trust the attached satisfactorily responds to the questions/issues raised in your August 4, 2000 approvable letter. Should you have any comments or questions regarding this submission, I can be reached at (908) 598-7821.

Sincerely,

Novartis Consumer Health, Inc.

for Nico C. Nicolaou
Manager, Regulatory Affairs

cc: Charles Ganley, M.D., Director, Division of OTC Drug Products (complete copy)
Dave Hilfiker, Project Manager, Division of Pulmonary Drug Products (cover letter)
Michael W. Rogers, FDA Kansas City District Office (Field Copy)

Submission dated 9/7/00

NCH Response to FDA Approvable Letter Dated August 4, 2000

NDA 21-082

Clemastine Fumarate / Acetaminophen / Pseudoephedrine Hydrochloride Tablets

---

1. Provide a suitable [redacted] test method [redacted] for determination of clemastine fumarate drug substance impurities. The [redacted] method, stated in the May 8, 2000, amendment as, " [redacted] " is inadequate. (Comment 1)

NCH Response:

Novartis Consumer Health commits to the development of a [redacted] method to replace the [redacted] method for certain impurities of the clemastine fumarate drug substance. We further commit to have the method developed, validated and submitted to FDA by 3/31/01.

APPEARS THIS WAY
ON ORIGINAL

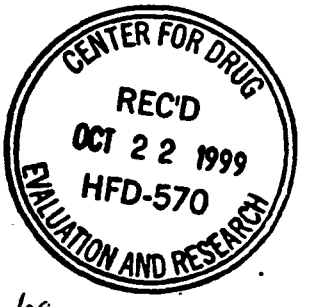
000061

Novartis Consumer Health, Inc.
560 Morris Avenue
Summit, NJ 07901-1312

Main Number: 908-598-7600
Fax: 908-273-2869

NOVARTIS

BC
ORIG AMENDMENT
DUPLICATE



October 20, 1999

Robert J. Meyer, M.D., Director
Division of Pulmonary Drug Products, HFD-570
Document Control Room 10B03
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

No review needed.
NAI
10/26/99

Re: Amendment to New Drug Application # 21-082
Clemastine fumerate/Acetaminophen/Pseudoephedrine Hydrochloride Tablets

Dear Dr. Meyer:

Reference is made to telephone conversations of 10/15/99 and 10/19/99 between Mr. Dave Hilfiker, Project Manager, FDA, Pulmonary Division and Novartis Consumer Health, Inc. (NCH). Mr. Hilfiker informed Novartis that while reviewing New Drug Application #21-082, he noticed that Form FDA 356h was incorrect and asked that the 505(b)(2) box be checked for this application. He stated that this application references two active ingredients, specifically pseudoephedrine HCl and acetaminophen, for which Novartis does not have right of reference. Additionally, Mr. Hilfiker also requested NCH add to the cross-reference section of the Form FDA 356h the NDA numbers for the pseudoephedrine and acetaminophen utilized in this application as well as to alter the Patent Certification Statement to reflect the 505(b)(2) status of this application.

Enclosed please a revised Form FDA 356h with the 505(b)(2) box now checked. Since the original NDA numbers for both pseudoephedrine HCl and acetaminophen were not available from the Orange Book or other sources and since the monographed product Theraflu® Sinus was used in the pharmacokinectic/bioavailability studies performed by Novartis, it has been added to the cross-reference section of the form. Theraflu® Sinus contains 30 mg of pseudoephedrine HCl and 500 mg of acetaminophen per tablet, is available Over-the-Counter, and meets amounts allowed in the tentative final monograph for OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Combination Drug Products.

If you have any questions please call the undersigned at (908) 598-7706.

Sincerely,
Novartis Consumer Health, Inc.

Vincent De Stefano

Vincent De Stefano
Associate Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Enclosures
cc: Dave Hilfiker, Project Manager

[redacted]

Application #(s):	NDA 21-082
Document Type:	NDA Letter
Document Group:	Information Request Letters
Document Name:	Discipline review letter for a pending NDA
Letter Code:	NDA-E2
COMIS Decision:	DR: DISCIPLINE REVIEW
Drafted by:	DH/December 18, 2000
Revised by:	HFD-570/Swiss HFD-570/Poochikian/12-18-00
Initialed by:	HFD-570/Barnes/12-18-00
Finalized:	HFD-570/Hilfiker/12-19-00
Filename:	C:\data\my documents\N21082\001218drltr
DFS Key Words:	
Notes:	
Linking Instructions:	Link this letter to the incoming documents that were reviewed.

[redacted]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-082

DISCIPLINE REVIEW LETTER

Novartis Consumer Health
560 Morris Avenue
Summit, NJ 07901-1312

Attention: Nico Nicolaou
Manager, Regulatory Affairs

Dear Mr. Nicolaou:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tavist Allergy/Sinus/Headache (clemastine fumarate, pseudoephedrine sulfate, and acetaminophen) Tablets.

We also refer to your submission dated September 7, 2000.

Our review of the CMC section of your submission is complete, and we have identified the following deficiencies.

Comment numbers in parentheses following these comments below refer to the Agency letter dated August 4, 2000.

1. Provide a progress report regarding a suitable ——— test method for determining clemastine fumarate drug substance impurities. (Comment 1)

[

]

e. Include the following commitment for the withdrawal provision found in the Agency's "Guidance for Industry: Submitting Documentation for the Stability of Human Drugs and Biologics," dated February 1987, on page 4. "Novartis will withdraw from the market any lots found to fall outside the approved specifications for the drug product. If there is evidence that the deviation is a single occurrence that does not affect the safety and efficacy of the drug product, it will be immediately discussed with the reviewing division and justification for the continued distribution of that batch will be provided. The change or deterioration in the distributed drug product will be reported, as required under 21 CFR 314.81(b)(1)(ii)."

[

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We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug 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 subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Mr. David Hilfiker, Regulatory Project Manager, at (301) 827-1084.

Sincerely yours,

Guirag Poochikian, Ph.D.
Chemistry Team Leader, DNDC II for
Division of Pulmonary and Allergy Drug Products (HFD-570)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

/s/

Guiragos Poochikian
12/19/00 04:54:31 PM

APPEARS THIS WAY
ON ORIGINAL

Document Information Page

This page is for FDA internal use only. Do NOT send this page with the Fax!

Application #(s):	NDA 21-082
Document Type:	NDA Telecon
COMIS Decision:	
Drafted by:	DH
Revised by:	
Initialed by:	HFD-570/Barnes/11-10-00 HFD-570/Meyer/11-27-00
Finaled:	HFD-570/Hilfiker/11-27-00
Filename:	C:\Data\My Documents\N21082\001106irfax.doc
DFS Key Words:	Fax; preliminary labeling comments
Notes:	
Linking Instructions:	Link this document to the incoming document the telecon concerns. If there is no such document, then link the document to the initial submission of the NDA or supplement, as appropriate.

END OF DOCUMENT INFORMATION PAGE

The Fax begins on the next page.

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 27, 2000

To: Nico Nicolaou	**From:** David Hilfiker
Company: Novartis Consumer Health, Inc.	Division of Division of Pulmonary and Allergy Drug Products
Fax number: 908-273-2869	**Fax number:** 301-827-1271
Phone number: 908-598-7821	**Phone number:** (301) 827-1084

Subject: Preliminary Labeling Comments

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ YES ☑ NO

APPEARS THIS WAY
ON ORIGINAL

Nico:

I reference our conversation of October 27, and your faxes of October 25 and 30, regarding your proposed labeling for NDA 21-082, Tavist Allergy/Sinus/Headache.

The Division of Over-the-Counter Drug Products has provided a review of the prototype labeling that you provided in the October 30 fax.

At this time, we have the following preliminary comments:

1. Remove the flag "New" from the principal display carton 6 months following the date of approval.

2. Ensure that the fax communication of October 25 is submitted in hard copy to the NDA.

We may have further labeling revisions to request prior to approval. The fact that we have no further comments at this time does not indicate any form of tentative approval of your labeling. We do not consider the labeling for this or any product to be approved until the NDA is approved.

If you have any questions, call me at (301) 827-1084.

David Hilfiker
Regulatory Project Manager

/s/

David Hilfiker
11/27/00 01:40:35 PM
CSO

SEP 27 2000

NDA 21-082

Novartis Consumer Health
560 Morris Avenue
Summit, NJ 07901-1312

Attention: Nico Nicolaou
Manager, Regulatory Affairs

Dear Mr. Nicolaou:

We acknowledge receipt on September 8, 2000 of your September 7, 2000, resubmission to your new drug application (NDA) for Tavist Allergy/Sinus/Headache (clemastine fumarate, pseudoephedrine sulfate, and acetaminophen) Tablets.

This resubmission contains additional information submitted in response to our August 4, 2000, action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is March 8, 2001.

If you have any questions, call Mr. David Hilfiker, Regulatory Project Manager, at (301) 827-1084.

Sincerely yours,

Sandy Barnes
Chief, Project Management Staff
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 21-082
HFD-570/Div. Files
HFD-570/Hilfiker
HFD-570/Barnes/9-19-00
HFD-570/Swiss/9-19-00
HFD-570/Poochikian/9-19-00
HFD-570/Lee
HFD-570/Chowdhury
HFD-570/Huff
HFD-570/Wilson
HFD-570/Wakelkamp
HFD-570/Choi
HFD-570/Meyer/9-19-00
DISTRICT OFFICE

/S/ 9/26/00
/S/ 9-21-00

Drafted by: HFD-570/Hilfiker/September 18, 2000
Final: HFD-570/Hilfiker/9-21-00
Filename: c:\data\my documents\N21082\000918acltr

CLASS 2 RESUBMISSION ACKNOWLEDGEMENT (AC)
(DDR: Update the user fee goal date based on the class of resubmission.)

APPEARS THIS WAY
ON ORIGINAL

Hilfiker
570

NDA 21-082

INFORMATION REQUEST LETTER

JUN 30 2000

Novartis Consumer Health
560 Morris Avenue
Summit, NJ 07901-1312

Attention: Nico Nicolaou
Manager, Regulatory Affairs

Dear Mr. Nicolaou:

Please refer to your new drug application (NDA) dated October 7, 1999, received October 8, 1999, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Tavist Allergy/Sinus/Headache (0.335 mg clemastine fumarate, 500 mg acetaminophen, and 30 mg pseudoephedrine hydrochloride) Tablets.

We also refer to your submissions dated May 8 and 18, 2000.

We have completed a CMC review of your submissions and have the following comments and information requests. Comment references in parentheses following these comments refer you to related comments in our April 5, 2000, letter. We need your prompt written response to continue our evaluation of your NDA.

1. Provide a suitable [redacted] test method [redacted]) for determination of clemastine fumarate drug substance impurities. [redacted] method, stated in the May 8, 2000, amendment as, [redacted]' is inadequate. (Comment 1)

T

J

WITHHOLD 2 PAGE (S)

If you have any questions, call Mr. David Hilfiker, Regulatory Project Manager, at (301) 827-1084.

Sincerely yours,

Guirag Poochikian, Ph.D.
Chemistry Team Leader
Division of Pulmonary and Allergy Drug Products (HFD-570)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 21-082
HFD-570/Div. Files
HFD-570/Hilfiker
HFD-570/Swiss/6-28-00
HFD-570/Poochikian
HFD-820/DNDC Division Director

/S/ 6/29/00
/S/ 6/30/00

Drafted by: HFD-570/Hilfiker/June 23, 2000
Initialed by: HFD-570/Barnes/6-28-00
HFD-570/Bertha (for Poochikian)/6-29-00
Final: HFD-570/Hilfiker/6-29-00
Filename: c:\my documents\N21082\000623irltr

/S/ 6/30/00

INFORMATION REQUEST (IR)

APPEARS THIS WAY
ON ORIGINAL

Hilfiker

Memorandum of Telephone Facsimile Correspondence

Date: June 1, 2000

To: Nico Nicolaou
Manager, Regulatory Affairs, Novartis Consumer Health

Fax No.: 908-273-2869

From: David Hilfiker
Project Manager

Subject: Information Request

# of Pages: 2

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.

/S/

David Hilfiker
Project Manager
Division of Pulmonary Drug Products

cc: Original NDA 21-082
HFD-570/Div File
HFD-570/Hilfiker
HFD-570/Wakelkamp
HFD-570/Uppoor

c:\my documents\N21082\000601irfax

Nico:

The following are the two items of information that we need for our ongoing review of your NDA 21-082 for Tavist Allergy/Sinus/Headache (per my voice mail message left for you today at 10 a.m.).

1. With regard to Study HSC-153B, analysis of the study samples of Clemastine:

   ALL INDIVIDUAL QUALITY CONTROL DATA (I.E. THE TWO MEASUREMENTS THAT CONSTITUTE EACH DUPLICATE) FOR EACH INDIVIDUAL ASSAY DAY AND MEAN INTRA-ASSAY PRECISION FOR EACH QUALITY CONTROL.

2. From the study report of study HSC-153B:

   FIGURES 1.1 AND 1.2
   2.1 AND 2.2
   3.1 AND 3.2

   IN ELECTRONIC FORMAT (PDF)

If you have any questions regarding these requests, contact me at 301-827-1084. Thanks.

Dave Hilfiker

/S/ 6/1/00

APPEARS THIS WAY
ON ORIGINAL

Hilfiker

Memorandum of Telephone Facsimile Correspondence

Date: April 25, 2000

To: Nico Nicolaou
Manager, Novartis Consumer Health Regulatory Affairs

Fax No.: 908-273-2869

From: David Hilfiker
Project Manager

Through: Barbara Elashoff, Biometrics Reviewer /S/
Steve Wilson, Biometrics Team Leader /S/

Subject: Information Request

# of Pages: 2

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.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 827-1050 and return it to us at 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

/S/

David Hilfiker
Project Manager
Division of Pulmonary Drug Products

cc: ORIG NDA 21-082
HFD-570/DIV FILE
HFD-570/HILFIKER
HFD-570/ELASHOFF
HFD-570/WILSON
HFD-570/LEE

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Nico:

We request the following information for our ongoing review of NDA 21-082, for Tavist Allergy/Sinus/Headache.

Regarding Tavist Study HSC-306,

Center #2 experienced delays due to:

- verification of inclusion/exclusion criteria;
- review of current medications;
- and collection of baseline allergy symptom evaluations (Volume 39, page 47).

Consequently, 36 patients received the first dose of their study medication 15-30 minutes late (Placebo: 8; T-F Sinus: 14; CTC: 14). Did the patients fill out the symptom assessments on time? Were the 9:00 AM assessments averaged in with the baseline assessments or treated as treatment period assessments?

Novartis performed the protocol-specified analyses: ANCOVA on the change from baseline MSC scores over the period of hours 2-5 postdose, using both "absolute value" and "percentage of the baseline MSC score." However, Novartis did not use the protocol-defined MSC score in this analysis. Instead, Novartis averaged runny nose-right and runny nose-left to form one symptom; and the same was done with itchy nose-right and itchy nose-left. The original MSC score definition more heavily weights these symptoms by assigning individual scores for both right and left nostrils. DPADP requests that Novartis provide the results of the protocol-specified analyses using the protocol definition of MSC score.

Please respond as soon as possible. Call me at (301) 827-1084 if you have questions.

Dave Hilfiker
Project Manager /S/ 4/25/00

APPEARS THIS WAY
ON ORIGINAL

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	0355
CONNECTION TEL	919082732869
SUB-ADDRESS	
CONNECTION ID	
ST. TIME	04/26 15:16
USAGE T	00'19
PGS.	2
RESULT	OK

Memorandum of Telephone Facsimile Correspondence

Date: April 25, 2000

To: Nico Nicolaou
Manager, Novartis Consumer Health Regulatory Affairs

Fax No.: 908-273-2869

From: David Hilfiker
Project Manager

Through: Barbara Elashoff, Biometrics Reviewer /S/
Steve Wilson, Biometrics Team Leader /S/

Subject: Information Request

# of Pages: 2

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.

Hilfiker

NDA 21-082

INFORMATION REQUEST LETTER

APR - 5 2000

Novartis Consumer Health
560 Morris Avenue
Summit, NJ 07901-1312

Attention: Nico Nicolaou
Manager
Regulatory Affairs

Dear Mr. Nicolaou:

Please refer to your October 7, 1999, new drug application for Tavist Allergy/Sinus/Headache (0.335 mg clemastine fumarate, 500 mg acetaminophen, 30 mg pseudoephedrine sulfate) Tablets.

We also refer to your submissions dated October 20, 1999, and March 1, 2000.

We are reviewing the CMC section of your submissions and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

WITHHOLD 3 PAGE (S)

Comments regarding the package labeling will be forthcoming after resolution of pending issues.

If you have any questions, call Mr. David Hilfiker, Project Manager, at (301) 827-1084.

Sincerely yours,

Guirag Poochikian, Ph.D.
Chemistry Team Leader for
Division of Pulmonary and Allergy Drug Products (HFD-570)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 21-082
HFD-570/Div. Files
HFD-570/Hilfiker /S/ 4-4-00
HFD-570/Swiss/4-4-00
HFD-570/Poochikian/4-4-00 /S/ - 4-5-00
HFD-560/Parmelee
HFD-820/DNDC Division Director /S/ 4/5/00
DISTRICT OFFICE

Drafted by: HFD-570/Hilfiker/April 3, 2000
Initialed by: HFD-570/Trout/4-4-00
Final: HFD-570/Hilfiker/4-4-00
Filename: c:\my documents\N21082\00-04-03.irltr.doc

INFORMATION REQUEST (IR)

APPEARS THIS WAY
ON ORIGINAL

Hilfiker

Memorandum of Telephone Facsimile Correspondence

Date: February 10, 2000

To: Nico Nicolaou
Manager, Regulatory Affairs
Novartis Consumer Health, Inc.

Fax No.: 908-273-2869

From: David Hilfiker
Project Manager

Subject: Information Request for NDA 21-082

# of Pages: 2

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.

/S/ 2/14/00
David Hilfiker
Project Manager
Division of Pulmonary Drug Products

c: ORIG NDA 21-082
HFD-570/ DIV FILE
HFD-570/ HILFIKER
HFD-570/ LEE
HFD-570/ WILSON
HFD-570/ ELASHOFF
HFD-560/ PARMELEE

e: my_documents\N21082\00-02-10.irfax.doc

Nico:

Please refer to your October 7, 1999, new drug application for Tavist Allergy/Sinus/Headache (0.335 mg clemastine fumarate/500 mg acetaminophen/30 mg pseudoephedrine hydrochloride) Tablets.

We are reviewing your submission and request the following additional information.

1. Provide a description of the font point sizes to be used on the carton/container labeling.

2. Electronic data needed for review of Studies HSC-305 and HSC-306

   - Demographics
   - All screening visit inclusion/exclusion criteria (include date of screening visit)
   - Treatment adherence (compliance) information
   - Study HSC-305: primary and secondary efficacy variables with dates of diary evaluations and visits
   - Study HSC-306: primary and secondary efficacy variables

   General Comments and Other Requests

   - Provide raw data and (in a separate dataset, if necessary) derived variables used in the analyses.
   - Provide the data in SAS Transport v.5 files. SAS Transport v.5 files are created by PROC XCOPY in Version 5 of SAS software and by the XPORT engine in Versions 6 and later. We are not able to archive other versions of SAS Transport files including those that are processed by the CPORT engine.
   - Provide definitions of each variable and definitions for the codes of the categorical variables. Explain how each of the derived variables was calculated.
   - Provide an annotated Case Report Form.

   You may provide this electronic information via diskette, CD-ROM, or zip disk.

   If you have any questions regarding our requests under item 2, please contact Steve Wilson (301-827-5583) or Barbara Elashoff (301-827-1073).

If you have any questions, call me at (301) 827-1084.

David Hilfiker
Regulatory Project Manager /S/

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	0184
CONNECTION TEL	919082732869
SUB-ADDRESS	
CONNECTION ID	
ST. TIME	02/14 22:45
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PGS.	2
RESULT	OK

Memorandum of Telephone Facsimile Correspondence

Date: February 10, 2000

To: Nico Nicolaou
Manager, Regulatory Affairs
Novartis Consumer Health, Inc.

Fax No.: 908-273-2869

From: David Hilfiker
Project Manager

Subject: Information Request for NDA 21-082

# of Pages: 2

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.

/S/ 2/14/00

Hilfiker

Memorandum of Telephone Facsimile Correspondence

Date: January 28, 2000

To: Nico Nicolaou
Manager, Regulatory Affairs
Novartis Consumer Health, Inc.

Fax No.: 908-273-2869

From: David Hilfiker
Project Manager

Subject: Information Request for NDA 21-082

# of Pages: 2

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.

cc: Orig NDA 21-082
HFD-570/Div File
HFD-570/Hilfiker
/Lee
/Chen
/Khorshidi

/S/ 2/1/00
David Hilfiker
Project Manager
Division of Pulmonary Drug Products

c:my_documents\N21082\00-01-28.hirfax.doc

Nico:

Please refer to your October 7, 1999, new drug application for Tavist Allergy/Sinus/Headache (0.335 mg clemastine fumarate/500 mg acetaminophen/30 mg pseudoephedrine hydrochloride) Tablets.

We are reviewing your submission and request the following additional information.

1. Provide the full address and appropriate CFN number for the manufacturing site for clemastine fumarate drug substance in Basel, Switzerland.

2. Provide CFN numbers for the following manufacturing sites:

   a. [redacted]

   b. [redacted]

   c. Drug product manufacturing facility at 10401 Highway 6, Lincoln, NE.

3. Submit individual data sets in electronic format (e.g., Excel spreadsheet or SAS transport files).

4. Provide subgroup analyses by gender, by race, and for ages greater than 65 years of the overall data presented in the ISS and ISE.

5. Provide any case reports related to an overdose of the drug product from clinical trials. Also, provide any spontaneous adverse event reports related to overdoses of marketed products containing clemastine fumarate.

6. Provide an electronic copy (MS Word file) of the proposed labeling.

If you have any questions, call me at (301) 827-1084.

David Hilfiker
Regulatory Project Manager

APPEARS THIS WAY
ON ORIGINAL

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	0144
CONNECTION TEL	919082732869
SUB-ADDRESS	
CONNECTION ID	
ST. TIME	02/02 05:11
USAGE T	00'19
PGS.	2
RESULT	OK

Memorandum of Telephone Facsimile Correspondence

Date: January 28, 2000

To: Nico Nicolaou
Manager, Regulatory Affairs
Novartis Consumer Health, Inc.

Fax No.: 908-273-2869

From: David Hilfiker
Project Manager

Subject: Information Request for NDA 21-082

# of Pages: 2

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.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 827-1050 and return it to us at 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

RECORD OF TELEPHONE CONVERSATION

Date:	October 27, 2000
Project Manager:	Hilfiker
Subject:	**Labeling Comment – Seal on Front Panel**
NDA:	21-082
Sponsor:	Novartis Consumer Healthcare
Product Name:	Tavist Allergy/Sinus/Headache Tablets

Novartis contacted the Agency several times in the month of October requesting feedback on the proposed labeling submitted in the September 7, 2000, class 2 resubmission to the August 4, 2000, approvable letter. Novartis' ultimate goal was to obtain a "tentatively approved" label in October that could be printed prior to approval in anticipation for product launch for the coming cough/cold season.

In each communication with Novartis, I emphasized that the Division of Pulmonary and Allergy Drug Products will not agree on a final label until the application is approved. Generally, labeling review and negotiation begins once all reviews are near to completion. Presently, there are CMC issues outstanding.

In an October 25, 2000, facsimile correspondence, Novartis acknowledged DPADP's concerns about a seal on the front panel that states ' ——— ' and proposed alternative language in the seal that states "Allergy & Sinus Relief." Novartis requested FDA comment on this proposal by Friday, October 27. They stated that they may print some packaging materials beginning on Monday, October 30, to have enough product on hand for an immediate launch. They are also assuming that the NDA will be approved in the near future, although the Agency has not given any indication that that will be the case.

TELECONFERENCE

Contact:	Nico Nicolaou, Regulatory Affairs Manager
Phone:	908-598-7821

I contacted Mr. Nicolaou to address the collective position of DPADP and DOTCDP regarding the seal on the front panel of the package labeling only. I stated that both Divisions have concerns over the use of a seal with the statement ——— but that neither Division has expressed concerns over the seal including a statement "Allergy & Sinus Relief." Mr. Nicolaou indicated that Novartis will most likely amend the label to include "Allergy & Sinus Relief" in place of ——— in the seal. I reminded Mr. Nicolaou to submit this amendment to the label to the NDA, with reference to this discussion.

I emphasized again that the FDA does not consider the labeling for this product to be approved until the NDA is approved. If Novartis decides to print labeling materials for launch prior to approval, they do so at risk of having to discard all of these materials in the event that DOTCDP

or DPADP ask for further modification to the labeling prior to approval. Novartis should not assume that any further modifications can be fulfilled as a post-approval commitment. Mr. Nicolaou acknowledged that the product must contain the approved labeling for distribution, or else it will be considered misbranded and may be recalled.

David Hilfiker
Project Manager

Attachment: 10-25-00 facsimile correspondence from Novartis (1 page, hard copy only)

Cc: Original NDA 21-082
HFD-570/Division file
HFD-570/Hilfiker, Swiss, Poochikian, Lee, Chowdhury, Wilson, Choi, Mann, Meyer
HFD-560/Merritt, Cook, Ganley, Katz, Hu, Chang, Ryland

Initialed by: HFD-570/Barnes/11-27-00

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/s/

David Hilfiker
11/27/00 01:49:02 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

Hilfiker

RECORD OF TELEPHONE CONVERSATION

Date:	August 2, 2000
Project Manager:	Hilfiker
Subject:	Response to CMC deficiency
NDA:	21-082
Sponsor:	Novartis Consumer Health
Product Name:	Tavist Allergy/Sinus/Headache

NDA 21-082, for Tavist Allergy/Sinus/Headache (clemastine fumarate, pseudoephedrine sulfate, and acetaminophen) Tablets, was submitted on October 7, 1999. The product is intended for direct-to-OTC market status once approved.

The applicant was issued a CMC information request letter on June 30, 2000. Comment 1 of that letter reads as follows:

Provide a suitable ——— test method (———————) for determination of clemastine fumarate drug substance impurities. The ——— method, stated in the May 8, 2000, amendment as, ——————————— ' is inadequate.

The applicant will not be able to respond to all deficiencies in the IR letter prior to the August 8, 2000, PDUFA action date for the NDA. Therefore, all of the deficiencies will be included as part of the NDA action.

The applicant has asked whether the Division will consider a proposal to address comment 1 as a Phase 4 commitment, as they anticipate being able to address the remainder of the deficiencies well in advance of the timetable for addressing comment 1.

After consultation with Kevin Swiss, CMC reviewer, I contacted the sponsor to inform them that they may propose a Phase 4 commitment in response to comment 1. The Division will not indicate at this time whether we will accept this information as a Phase 4 commitment. The Division may consider the response to this comment adequate for filing if the applicant provides a reasonably short time frame for fulfillment of the proposed Phase 4 commitment. If the Division files the submission as a complete response, that does not indicate that a Phase 4 commitment will be acceptable for comment 1. The determination of whether this information can be supplied as a Phase 4 commitment or must be supplied prior to approval will be a review issue.

David Hilfiker
Project Manager

/S/ 8/4/00

Cc: Original NDA 21-082
HFD-570/Division file
HFD-570/Hilfiker
HFD-570/Swiss/8-3-00
HFD-570/Poochikian/8-3-00

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WITHHOLD 2 PAGE (S)

1. *Provide a suitable [redacted] method [redacted]) for determination of clemastine fumarate drug substance impurities. The [redacted] method, stated in the May 8, 2000, amendment as, [redacted] is inadequate.*

Dr. Swiss clarified that [redacted] is an outdated method. Dr. Swiss requested that Novartis develop a method derived in more modern technology to obtain more accurate assay measurements.

David Hilfiker
Project Manager

/S/ 8/14/00

Attachment: (1) July 24, 2000, facsimile correspondence from Novartis to FDA
33 pages, hard copy only

Cc: Original NDA 21-082
HFD-570/Division file
HFD-570/Hilfiker
HFD-570/Swiss/8-3-00/8-4-00
HFD-570/Poochikian/8-3-00
HFD-570/Wakelkamp
HFD-570/Choi

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WITHHOLD 33 PAGE (S)

Hilfiker

RECORD OF TELEPHONE CONVERSATION

Date:	June 26, 2000
Project Manager:	Hilfiker
Subject:	**Drug Substance Manufacturing Site Inspections**
NDA:	21-082
Sponsor:	Novartis Consumer Health, Inc.
Product Name:	Tavist Allergy/Sinus/Headache Tablets

NDA 21-082 was submitted on October 7, 1999, received on October 8, 1999. It provides for a triple combination tablet consisting of acetaminophen, pseudoephedrine sulfate, and clemastine hydrochloride, in doses suitable for an over-the-counter product. The application PDUFA due date is August 8, 2000.

[redacted]

Novartis asked to speak to representatives of the Division about the possible action for this NDA with an outstanding inspection.

DPADP Participants:	David Hilfiker	Project Manager
	Martin Himmel	Deputy Division Director
	Kevin Swiss	CMC Reviewer
Novartis Participants:	Edith Lewis-Rogers	Quality Assurance in Scientific Affairs
	Nico Nicolaou	Regulatory Affairs
	Henry Weidmuller	Regulatory Affairs

Novartis stated that they wanted clarification on whether a Not Approvable (NA) action or an Approvable (AE) action would be issued based on an outstanding inspection, if there were no other review deficiencies.

Dr. Himmel stated that the Division does not comment on an action prior to issuance of the letter, and no indication of the action for this NDA will occur in this teleconference. However, in general, the Division issues a Not Approvable (NA) action when there are deficiencies that may require a significant period of time to address or when new clinical trials are required. Otherwise, the Division uses Approvable (AE) in most cases. The action depends on the nature of the deficiencies.

Novartis stated that [redacted] anticipates being ready for another inspection at the end of July. Mr. Hilfiker stated that the Division is continuing to review the application and may issue an action prior to the inspection, certainly by the August 8, 2000, PDUFA due date.

Cc: Original NDA 21-082
HFD-570/Division file
HFD-570/Hilfiker
HFD-570/Swiss/6-27-00
HFD-570/Himmel/7-6-00

/S/ 7/10/00

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Hilfiker

RECORD OF TELEPHONE CONVERSATION

Date:	March 28, 2000
Project Manager:	Hilfiker
Subject:	Review Questions
NDA:	21-082
Sponsor:	Novartis Consumer Health
Product Name:	Tavist Cold/Allergy/Sinus Tablets

PARTICIPANTS:

FDA:	Barbara Elashoff	Biostatistics
	David Hilfiker	Project Management
	Steve Wilson	Biostatistics
Novartis:	Morris Gold	Biostatistics
	Nico Nicolaou	Regulatory Affairs

Regarding Study 305, the statistical reviewer, Ms. Elashoff, had several questions about study report references of reported p-values for particular analyses and the sponsor's application of diary data "windows." The sponsor provided these study report page references and details concerning the data "windows." In addition, as somnolence and fatigue are known side effects of the drug, Ms. Elashoff asked that the sponsor calculate the number of patients in Study 305 with at least one adverse effect after excluding these known effects. The sponsor responded that they would resubmit Table 19.1, discounting somnolence and fatigue as adverse events.

For Study 306, Ms. Elashoff requested clarification regarding the eligibility criteria for baseline symptom severity. The cutoff value of 18 seemed low for the sum of the three baseline evaluations, and the wording in the case report form seemed indicated of a cutoff of 18 for *each individual evaluation*, not the *sum* of the three evaluations. The sponsor confirmed that it was intended that the cutoff value was to be the sum of the three evaluations. Related to this issue, the sponsor stated that the baseline means displayed in the table on page 47 of Volume 39 are the *mean* of the average of the three pre-treatment assessments for each patient (not the *sum*).

David Hilfiker /S/ 4-24-00
Project Manager

Cc: Original NDA 21-082
HFD-570/Division file
HFD-570/Hilfiker
HFD-570/Elashoff/4-24-00
HFD-570/Wilson/4-24-00
HFD-570/Lee
HFD-570/Chowdhury

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HFD-570
HFLFIKE12

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

AUG 23 2000

[ ]

Dear Mr. —

On June 23, 2000, Mr. Chad E. Schmear, representing the Food and Drug Administration (FDA), conducted an inspection of ———————————— (———————————— . This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to ensure the proper conduct of clinical studies for submission to FDA, and the protection of the rights and welfare of human subjects.

This inspection focused on Protocol HSC-306: "A multi-center, double-blind, double-dummy, placebo-controlled, randomized, parallel group study to evaluate the safety and efficacy of clemastine 0.5 mg q.i.d. vs clemastine 1.0 mg b.i.d. vs. placebo for allergy symptom relief."

From our evaluation of the inspection report and your oral responses to the inspectional observations, we conclude that you did adhere to pertinent federal regulations and/or good clinical investigational practices governing sponsor responsibilities for the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Schmear during this inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

[redacted]

APR 19 [redacted]

Between March 14 and 16, 2000, Mr. Carl J. Montgomery, representing the Food and Drug Administration (FDA) inspected your conduct as the investigator of record of clinical studies (protocols #HSC-151, 152, 153b, and 303) of Tavist® (clemastine fumerate) Tablets that you conducted for Novartis Consumer Health, Inc. From our evaluation of the inspection report prepared by Mr. Montgomery and your oral responses to the inspectional observations, we conclude that you conducted your study in compliance with applicable Federal regulations and good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects.

This inspection is part of FDA's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

We appreciate the cooperation shown Mr. Montgomery during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Medical Policy, HFD-45
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, MD 20855

cc: [redacted]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAR 24 ' '

Linda B. Ford
The Asthma & Allergy Center, P.C.
401 E. Gold Coast Road, Suite 124
Papillion, NE 68046

Dear Dr. Ford:

Between February 29 and March 2, 2000, Mr. Carl J. Montgomery, representing the Food and Drug Administration (FDA) inspected your conduct as the investigator of record of a clinical study (protocol #HSC-306) of Tavist® (clemastine fumerate) Tablets that you conducted for Novartis Consumer Health, Inc. From our evaluation of the inspection report prepared by Mr. Montgomery and your oral responses to the inspectional observations, we conclude that you conducted your study in compliance with applicable Federal regulations and good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects.

This inspection is part of FDA's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

We appreciate the cooperation shown Mr. Montgomery during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Medical Policy, HFD-45
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, MD 20855

Div. File

JAN 24 1997

Meeting Date: December 9, 1996 **Time**: 9:00-10:30 AM
Location: Conference Room "O" **IMTS #**: 439
Sponsor: Sandoz Pharmaceuticals

Product: clemastine/pseudoephedrine/acetaminophen (CTC)
Type of Meeting: pre-NDA

FDA Attendees:

Michael T. Benson	Regulatory Review Pharmacist, HFD-560
Lindsay Cobbs	Project Manager, HFD-570
Dale Conner	Clinical Pharmacology, Team Leader
Rosemary Cook	Supervisory Project Manager, HFD-560
Misoon Chun	Pharmacology Reviewer, HFD-570
James Gebert	Statistical Reviewer, HFD-570
William Gilbertson	Associate Director for OTC Drug Monograph HFD-105
Brad Gillespie	Clinical Pharmacology Reviewer
Linda Hu	Medical Officer, HFD-560
Parinda Jani	Project Manager, HFD-570
John K. Jenkins	Division Director, HFD-570
Susan Johnson	Medical Officer, HFD-570
Linda Katz	Deputy Division Director, HFD-560
Michael D. Kennedy	Team leader, HFD-560
Cazemiro R. Martin	Chemistry Reviewer, HFD-560
Babette Merritt	Project Manager, HFD-560
Robert Meyer	Clinical Team Leader, HFD-570
Elizabeth Ryland	Chemistry Reviewer, HFD-560
Vibhakar Shah	Chemistry Reviewer, HFD-570
Hillary Sheevers	Pharmacology Team Leader, HFD-570

Sandoz Pharmaceutical Attendees:

Michael Carroll	Director, Marketing
Lori Beth Cirangle	Associate Director, Medical
Margaret Flory	Associate Director, Regulatory Affairs
Mark Gelbert	Executive Director, Scientific Affairs
Nico Nicolaou	Regulatory Specialist
Robert O'Connor	Associate Director, Clinical Research
Horst Schran	Director, Biopharmaceutics
Michael Smith	Manager, Marketing

Background: See sponsor's submissions dated October 15 and November 14, 1996, Medical Officer's review dated December 12, 1996, and Clinical Pharmacology and Biopharmaceutics Review dated December 17, 1996.

Ms. Flory gave an overview of the clinical development program for the clemastine triple combination (CTC) product, and the rationale to combine the three ingredients.

Dr. Gillespie described various problems with the bioequivalence studies.

In multi-dose study HSC-151, bioequivalence was demonstrated between clemastine 1 mg, and 0.5 mg tablets. However, there are no single-dose studies conducted to demonstrate bioequivalency between 1 mg, and two 0.5 mg clemastine tablets. Multiple-dose bioequivalency studies lack the sensitivity of single-dose studies for detection of bioequivalency differences. Thus, the efficacy of a single-dose of 0.5 mg clemastine needs to be demonstrated.

In study HSC-302, the 0.5 mg clemastine tablet was compared to 1 mg of clemastine service tablet, and 1 mg of clemastine marketed tablet. This study does not address the issue of dose interchangeability between the marketed and service tablets of clemastine. The 0.5 mg tablet was proportionally more bioavailable than the 1 mg tablet (analyzed as service and marketed tablet together).

In study HSC-152, the 0.5 mg service tablet and the proposed CTC product were compared to approved reference products, i.e., Thera-Flu Sinus, and clemastine syrup. Bioequivalence of pseudoephedrine and acetaminophen components of CTC and Thera-Flu Sinus was demonstrated. Clemastine bioequivalence between the 0.5 mg service tablet and the clemastine syrup was demonstrated, however, bioequivalence for clemastine between the CTC and other clemastine formulations was not demonstrated. Although this study shows a lack of effect of clemastine on the bioavailabilities of pseudoephedrine and acetaminophen, this study does not address the potential effect of acetaminophen and pseudoephedrine on clemastine bioavailability.

The sponsor claims that bioequivalency was not demonstrated due to the low plasma levels (near LOQ) from the 0.5 mg product. This was questioned primarily because bioequivalence was demonstrated between the 0.5 mg tablet and syrup.

To address the issue of possible different bioavailabilities of different clemastine formulations, the sponsor has proposed to conduct study HSC-153, a single-dose bioavailability study. The proposed doses, 4 CTC tablets compared to 2 service tablets or 1

mg of clemastine syrup, are acceptable from the safety standpoint. However, the Agency recommends the following protocol modification.

CURRENT PROTOCOL	REVISED PROTOCOL
Trt A: CTC	Trt A: CTC
Trt B: Syrup	Trt B: Service Tablet and Thera-Flu
Trt C: Service Tablet	Trt C: Service Tablet
	Trt D: Syrup (optional)

The bioavailability of all three components should be evaluated. The modified protocol will address the issue of drug interaction, will link the CTC product to the service tablet used in clinical studies, and if treatment arm D is included, will link the CTC product to the currently marketed syrup formulation. The Division concurred that the proposed dose-doubling (equivalent to 1 mg of clemastine) is acceptable.

Dr. Johnson stated that the clemastine products are neither included in the OTC monograph for antihistamines, nor for combinations. The CTC product will have to meet the regulatory requirements for fixed combinations, demonstrating contribution of each component, as described in 21 CFR 300.50. Also, the —— indication is not supported for clemastine. The Division has concerns regarding the lowest effective dose of clemastine, since the dose response component was only included in study HSC-303, the wheal and flare trial. This model has limited clinical relevance.

It is unclear that the correct dosing interval for clemastine, i.e., every 6 hours, has been determined. Since the half-life of clemastine is 20 hours, the Division is concerned about the safety of 0.5 mg clemastine administered every 6 hours. In study HSC-304, instead of random sequence, each patient received placebo during the fourth treatment period. This makes it impossible to separate sequence treatment effects and limits utility of these data. Sandoz will include the dosing interval compliance data for study HSC-305, and individual adverse events data in the final study report.

The Division of Over the Counter Drug Products (DOTCDP) would like Sandoz to provide justification for the inclusion of an "allergy" indication in their proposed labeling. The phrase "pain reliever/fever reducer" should be included in the statement of identity. As the headache related to ——— may not last for 7 days, justification for including the high dose of acetaminophen needs to be provided. Alternatively, the WARNINGS section may include a statement stating that ——— A warning regarding the concomitant use of alcohol and acetaminophen should be included. Sandoz objects to labeling requirements that are not consistent with the OTC cough-cold combination tentative final monograph. This issue will be discussed further when the draft labeling is submitted.

Dr. Shah stated that the CMC part of the submission should be complete as per the NDA requirement. CMC information regarding the drug substance clemastine fumarate must be provided by reproducing the data from the cross-referenced NDA or by providing exact location of the data, e.g., volume number, page number, in the cross-referenced NDA. Depending on the observed stability data, the drug substance specifications may need to be updated. Letters of Authorization for various DMFs pertaining to the ——— must be provided. The clinical batches and to-be-marketed batches for the drug product should be identified clearly in the submission. The sponsor claims that no formulation changes were made during development.

Sandoz has agreed to revise the protocol for study HSC-153. Further, Sandoz has agreed to submit a protocol to determine the onset of action of clemastine 0.5 mg. It was suggested that exposure chamber or "day in the park" designs be considered. The Division will require data for the first dose efficacy for clemastine in order that it be considered with acetaminophen.

/S/

Parinda Jani

Project Manager

CC:

DIV FILE/HFD-570
HFD-570/SCHUMAKER/1-2-97
HFD-570/JOHNSON/1-2-97
HFD-570/MEYER/1-3-97
HFD-570/GILLESPIE/1-3-97
HFD-570/CONNER/1-3-97
HFD-570/SHAH/1-3-97
HFD-560/ATTENDEES/1-10-97