CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-082

ADMINISTRATIVE DOCUMENTS

~~CORRESPONDENCE~~

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-082 /SE_____ - _____

Drug Tavist Allergy/Sinus/Headache Caplets Applicant Novartis Consumer Health

RPM Hilfiker Phone 301-827-1084

☐505(b)(1)
☑505(b)(2) Reference listed drug Tavist-1 Tablets; Thera-Flu Sinus

☐Fast Track ☐Rolling Review Review priority: ☑ S ☐P

Pivotal IND(s) —

Application classifications:
Chem Class _____
Other (e.g., orphan, OTC) OTC

PDUFA Goal Dates:
Primary March 8, 2001
Secondary same

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: ☑ User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption

- Action Letter..... ☑AP ☐ AE ☐NA

- Labeling & Labels
  FDA revised labeling and reviews..... OTC review pending
  Original proposed labeling (package insert, patient package insert) ..... Yes
  Other labeling in class (most recent 3) or class labeling..... No
  Has DDMAC reviewed the labeling? ..... ☐ Yes (include review) ☑ No
  Immediate container and carton labels ..... Yes
  Nomenclature review ..... Yes

- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ☑ is not on the AIP.
  Exception for review (Center Director's memo)..... _____
  OC Clearance for approval..... _____

Continued ⇨

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) ☑ Materials requested in AP letter

- Post-marketing Commitments — yes
  - Agency request for Phase 4 Commitments..... — No
  - Copy of Applicant's commitments ..... — Yes

- Was Press Office notified of action (for approval action only)?..... ☐ Yes ☑ No
  - Copy of Press Release or Talk Paper.....

- Patent
  - Information [505(b)(1)] .....
  - Patent Certification [505(b)(2)]..... — Yes
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)]..... — No

- Exclusivity Summary ..... — Yes

- Debarment Statement ..... — Yes

- Financial Disclosure
  - No disclosable information ..... — Yes
  - Disclosable information – indicate where review is located .....

- Correspondence/Memoranda/Faxes ..... — Yes

- Minutes of Meetings ..... — Yes
  - Date of EOP2 Meeting No
  - Date of pre NDA Meeting 12-9-96
  - Date of pre-AP Safety Conference N/A

- Advisory Committee Meeting ..... — N/A
  - Date of Meeting .....
  - Questions considered by the committee .....
  - Minutes or 48-hour alert or pertinent section of transcript .....

- Federal Register Notices, DESI documents ..... — N/A

CLINICAL INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) ..... — complete ~~pending~~
- Clinical review(s) and memoranda ..... — Yes

Continued ⇨

- Safety Update review(s) ...not requested because of OTC marketing of two active ingredients and estimated lack of new safety information on clemastine since the time of original NDA submission — N/A

- Pediatric Information
  ☑ Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred See Clin Section
  Pediatric Page..... Yes
  ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted ☑ Not Applicable

- Statistical review(s) and memoranda ..... Yes

- Biopharmaceutical review(s) and memoranda..... Yes

- Abuse Liability review(s) ..... N/A
  Recommendation for scheduling .....

- Microbiology (efficacy) review(s) and memoranda ..... N/A

- DSI Audits ..... complete
  ☑Clinical studies ☑ bioequivalence studies .....

CMC INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- CMC review(s) and memoranda ..... Yes

- Statistics review(s) and memoranda regarding dissolution and/or stability ..... pending

- DMF review(s) ..... Yes

- Environmental Assessment review/FONSI/Categorical exemption ..... Pp 52-53, review #1

- Micro (validation of sterilization) review(s) and memoranda ..... N/A

- Facilities Inspection (include EES report)
  Date completed 1-2-01 ..... ☑ Acceptable ☐ Not Acceptable

- Methods Validation ..... ☐ Completed ☑ Not Completed

PRECLINICAL PHARM/TOX INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- Pharm/Tox review(s) and memoranda ..... Yes

Continued ⇨

- Memo from DSI regarding GLP inspection (if any) ..... N/A

APPEARS THIS WAY
ON ORIGINAL

Continued ⇨

- Statistical review(s) of carcinogenicity studies ..... N/A
- CAC/ECAC report ..... N/A

APPEARS THIS WAY
ON ORIGINAL

DOTCDP
Labeling Reviews

APPEARS THIS WAY
ON ORIGINAL

Labeling Review of NDA – Addendum

NDA # 21-082

Submission Dates: 9/7/, 10/25* and 30*/00
Review Date: 10/31/00

APPLICANT: Novarits Consumer Health, Inc
560 Morris Avenue
Summit, NJ 07901-1312

DRUG: **TAVIST® Allergy/Sinus/Headache Caplets**
[acetaminophen 500mg, clemastine fumarate 0.335 (equivalent to 0.25 mg clemastine) and pseudoephedrine HCl 30 mg tablets]

PHAMACOLOGIC CATEGORY: Pain reliever/fever reducer/antihistamine/nasal decongestant

SUBMITTED: Carton labels for 24's and blister package

REVIEWER'S COMMENT:
An "Approvable" letter was sent to the sponsor on August 4, 2000 contingent upon certain revisions of the labeling.

Sponsor has complied with all requests as stated in the Agency's August 4, 2000 letter as follows:

1. Added "capsule-shaped tablet" as a footnote on the principal display panel under declaration of net content.
2. Removed ——— on the front panel.
3. Replace ' ——— " seal on the principal display panel with "Sinus/Allergy Relief" seal as stated in the fax submission dated October 25, 2000.
4. Revised the 24s carton and blister labeling according to the prototype. The sponsor did not submit revised carton label for the 48s.

RECOMMENDATIONS:
1. The draft carton label for 24s faxed on October 30, 2000 and draft blister package labeling submitted on September 7, 2000 are acceptable. An Approval letter can be issued requesting final printed labeling identical to the draft labeling submitted.
2. Inform the sponsor that the flag "New" on the principal display panel is to be removed after 6 moths after marketing.
3. The sponsor has submitted the draft carton labels for the 48s in the original submission. If the sponsor is planning to market the 48s, the labeling for this packaging should be identical to the labeling for the 24s submitted on October 30, 2000.

/S/
Bettie Ryland, IDS

/S/
Marina Chang, R. Ph., Leader, Team 1

CC:
HFD-560/Director /S/ -11/2/00
HFD-560/Deputy Director
HFD-560/MO
HFD-/560/Team 1 leader
HFD-560/IDS

APPEARS THIS WAY
ON ORIGINAL

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

Tel 908 598-7600
Fax 908 273-2869

NOVARTIS

FAX

Date:	October 30, 2000
To:	Dave Hilfiker, Project Manager, Division of Pulmonary Drug Products
Company:	Food and Drug Administration
From:	Nico Nicolaou, Manager, DRA
# of Pages (Including Cover)	3 RE: Tavist Allergy/Sinus/Headache Tablets NDA 21-082

Dear Dave:

Pursuant to our telephone conversation of Friday 27 October during which we talked about the seal statement on the front panel of the carton for the subject product, you informed me that the Agency (Pulmonary and OTC Drug Divisions) have agreed to permit Novartis Consumer Health (NCH) to retain the seal, provided that NCH utilize the term 'Allergy & Sinus Relief' and remove the wording ——— In addition you had asked that NCH send a copy of the labeling reflective of this modification as well as any other changes.

As requested, I have attached a copy of the carton labeling (enlarged @ 130%) for your review. A normal copy (@ 100% print size) will also be submitted to your attention as part of the NDA file.

Please advise of any comments or concerns you may have by 4 PM this Wednesday.

If you have any questions, I can be reached at (908) 598-7821 or Fax (908) 273-2869.

Sincerely,

Nico

Nico C. Nicolaou
Manager, Regulatory Affairs

Cc: Babette Merritt, Project Manager, Division of OTC Drug Products

Prototype Labeling for Tavist Alleryg/Sinus/Headache Caplets

A. CARTON

TOP PANEL:
Tamper Evident Feature: Tavist Allergy/Sinus/Headache Caplets are sealed in individual caplet packages. Use only if the individual caplet seal is unbroken.

Novartis (logo)
Novartis Consumer Health, Inc.
Summit, NJ 07901-1312 ©1999
0000-00

Tavist® (logo) Antihistamine / Nasal Decongestant / Pain Reliever
ALLERGY/SINUS/HEADACHE

Caplet (photo)
24 **CAPLETS**

PRINCIPAL DISPLAY PANEL:
Antihistamine / Nasal Decongestant / Pain Reliever

Tavist® ALLERGY/SINUS/HEADACHE
(acetaminophen 500 mg, clemastine fumarate 0.335 mg (equivalent to 0.25 mg clemastine) and pseudoephedrine HCl 30 mg tablets)

- Sinus congestion & pressure
- Runny nose & sneezing
- Itchy, watery eyes
-
- Itchy throat

Caplet (photo)

24 CAPLETS

RIGHT SIDE PANEL:

UPC
Lot:
Exp.

Warnings

Stop use and ask a doctor if
- symptoms continue or get worse
- new or unexpected symptoms occur
- nervousness, dizziness or sleeplessness occurs
- a fever lasts for more than 3 days
- nasal congestion lasts for more than 7 days

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a poison control center right away. Prompt medical attention is critical for adults as well as children even if you do not notice any signs or symptoms.

24 CAPLETS®
"capsule-shaped tablet"

- Sinus congestion & pressure
- Runny nose & sneezing
- Itchy, watery eyes
- Itchy throat

ALLERGY & SINUS RELIEF

ALLERGY/SINUS/ HEADACHE

New!

TAVIST®

Clemastine fumarate 0.335 mg (equivalent to 0.25 mg clemastine), pseudoephedrine HCl 30 mg tablets, and acetaminophen 500 mg

Antihistamine / Nasal Decongestant / Pain Reliever / Fever Reducer

Drug Facts (continued)

Directions
- adults and children 12 years of age and over: take 2 caplets every 6 hours as needed; not more than 8 caplets in 24 hours unless directed by a doctor
- children under 12 years of age: ask a doctor

Other information
- store at 20°-25°C (68°-77°F)
- avoid excessive heat

Inactive ingredients calcium sulfate, glyceryl behenate, maltodextrin, methylcellulose, methylparaben, polyethylene glycol, silicon dioxide, sodium lauryl sulfate, starch, titanium dioxide

Questions call 1-800-452-8051 24 hours a day, 7 days a week.

24 CAPLETS®

TAVIST®

Tamper Resistant Feature: Total Allergy/Sinus/Headache Caplets are sealed in individual cotton packages. Use only if the individual outer seal is unbroken.

Allergy/Sinus / Nasal Decongestant / Pain Reliever / Fever Reducer

Drug Facts

Active Ingredients (in each tablet) — Purpose

Acetaminophen 500 mg	Pain reliever/fever reducer
Clemastine fumarate 0.335 mg (equivalent to 0.25 mg clemastine)	Antihistamine
Pseudoephedrine HCl 30 mg	Nasal decongestant

Uses temporarily relieves these symptoms of hay fever or other upper respiratory allergies, and common cold:
- sinus congestion and pressure
- headaches
- sneezing
- itching of the nose or throat
- fever
- nasal congestion
- itchy watery eyes
- runny nose
- minor aches and pains

Warnings

Alcohol Warning: If you consume 3 or more alcoholic drinks daily, ask your doctor whether you should take acetaminophen or other pain relievers/fever reducers. Acetaminophen may cause liver damage.

Do not use if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.

Ask a doctor before use if you have
- heart disease
- high blood pressure
- thyroid disease
- diabetes
- glaucoma
- a breathing problem such as emphysema or chronic bronchitis
- trouble urinating due to an enlarged prostate gland

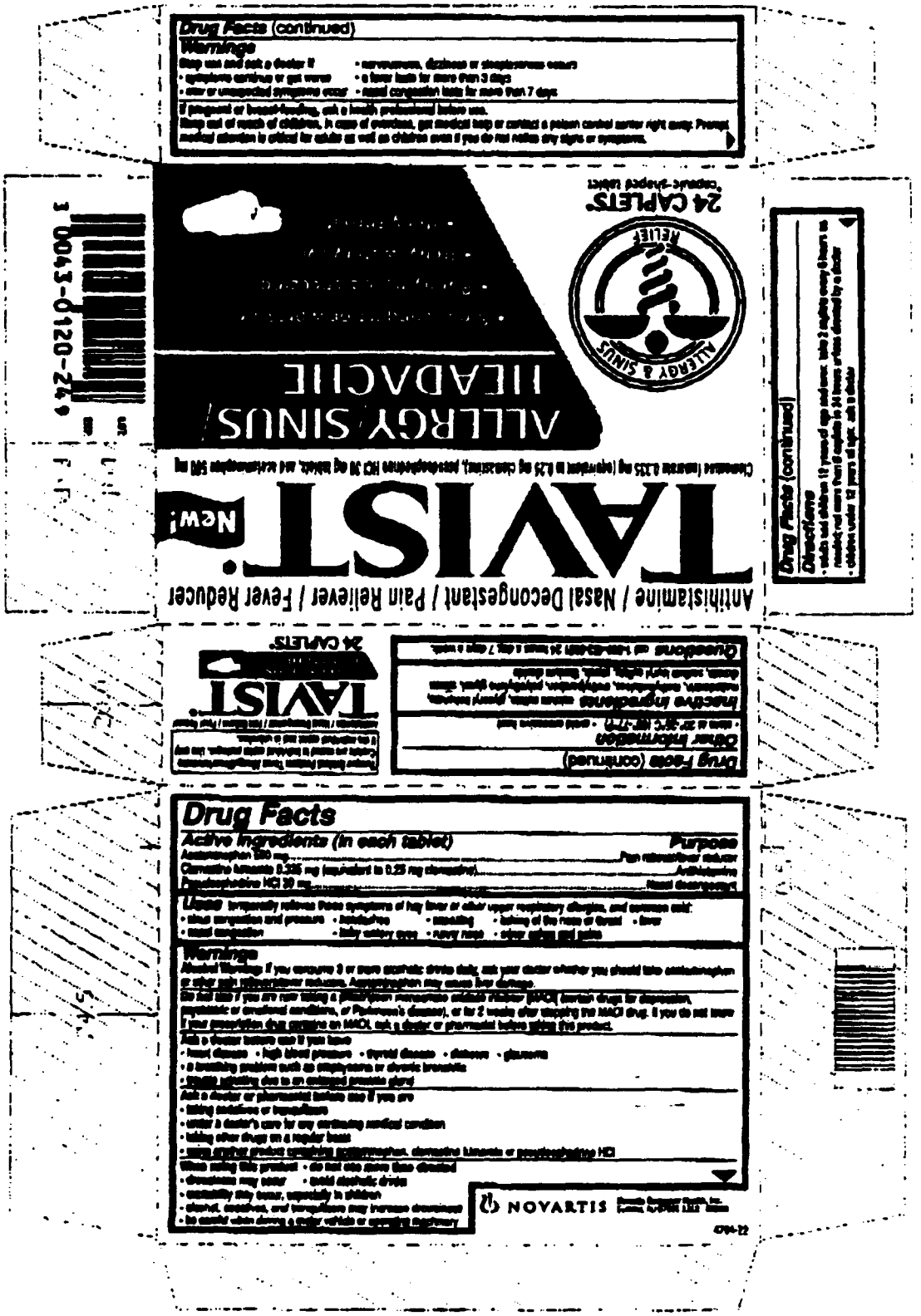
Ask a doctor or pharmacist before use if you are
- taking sedatives or tranquilizers
- under a doctor's care for any continuing medical condition
- taking other drugs on a regular basis
- using another product containing acetaminophen, clemastine fumarate or pseudoephedrine HCl

When using this product
- do not use more than directed
- drowsiness may occur
- avoid alcoholic drinks
- excitability may occur, especially in children
- alcohol, sedatives, and tranquilizers may increase drowsiness
- be careful when driving a motor vehicle or operating machinery

NOVARTIS

4704-22

printed @ 130%


Drug Facts (continued)
Warnings
24 CAPLETS.
ALLERGY SINUS HEADACHE
TAVIST.
New!
Antihistamine / Nasal Decongestant / Pain Reliever / Fever Reducer
Drug Facts (continued)
Directions
Drug Facts (continued)
Other Information
Inactive Ingredients
Questions or comments?
24 CAPLETS.
TAVIST.
Drug Facts
Active Ingredients (in each tablet)
Purpose
Uses
Warnings
Ask a doctor before use if you have
Ask a doctor or pharmacist before use if you are
When using this product
NOVARTIS

printed @ 100%

HILFIKER

LABELING REVIEW OF NDA

JUN 26 2000

NDA #: 21-082

Submission Date: 10/20/99
Review Date: 04/28/00

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

DRUG: **TAVIST® Allergy/Sinus/Headache Caplets (acetaminophen 500 mg, clemastine fumarate 0.335 mg (equivalent to 0.25 mg clemastine) and pseudoephedrine HCl 30 mg tablets)**

PHARMACOLOGIC CATEGORY: **Pain reliever/fever reducer/antihistamine/nasal decongestant**

SUBMITTED: **Carton labels for 24's and 48's and blister package**

Reviewer's Comments:

Clemastine fumarate (an antihistamine) is approved under an NDA for the treatment of allergy and hay fever symptoms. Currently, there is only one OTC combination cold/cough drug products on the market containing clemastine fumarate with phenylpropanolamine HCl, a nasal decongestant. The Sponsor is now seeking approval of clemastine fumerate in combination with pseudoephedrine (a nasal decongestant) and acetaminophen (an analgesic) as a triple combination product.

Sponsor provided some but not all of the labeling and font size specifications and has been asked to comply with our request for a complete set of specifications. Review of the laeling and font size specifications is pending receipt of such information from the Sponsor.

The sponsor employed the Drug Fact format and utilized bulleting but did not adhere to the appropriate alignment of the bullets in those subsections under "WARNINGS."

Reviewer recommended additions are identified by "redline" (shaded text) and deletions by "strike out."

APPEARS THIS WAY
ON ORIGINAL

A. CARTON

TOP PANEL:
Tamper Evident Feature: Tavist Allergy/Sinus/Headache Caplets are sealed in individual caplet packages. Use only if the individual caplet seal is unbroken.

Novartis (logo)
Novartis Consumer Health, Inc.
Summit, NJ 07901-1312 ©1999
0000-00

Tavist® (logo) Antihistamine / Nasal Decongestant / Pain Reliever
ALLERGY/SINUS/HEADACHE
Caplet (photo)
24 **CAPLETS**

PRINCIPAL DISPLAY PANEL:
Antihistamine / Nasal Decongestant / Pain Reliever
Tavist® ALLERGY/SINUS/HEADACHE
(acetaminophen 500 mg, clemastine fumarate 0.335 mg (equivalent to 0.25 mg clemastine) and pseudoephedrine HCl 30 mg tablets)
Reviewer's Comment: We recommend inclusion of the established names as part of the Statement of Identity [21 CFR 201.61(b)].

- Sinus congestion & pressure
- Runny nose & sneezing
- Itchy, watery eyes
- Itchy throat

Caplet (photo)

Reviewer's Comment: This seal may mislead the consumer into thinking that this product is more reliable than other marketed products. We recommend this seal be removed unless Sponsor can show there is substantiated reason to include it.

24 **CAPLETS**

RIGHT SIDE PANEL:

UPC
Lot:
Exp.

BACK, BOTTOM AND LEFT SIDE PANELS:

Drug Facts

Active Ingredients (in each caplet) **Purpose**

Acetaminophen 500 mg.....Pain Reliever/Fever reducer
Clemastine fumarate 0.335 mg (equivalent to 0.25 mg of clemastine).....Antihistamine
Pseudoephedrine HCl 30 mg.....Nasal Decongestant

Reviewer's Comments: Section 201.66(d)(1) of the Labeling Rule requires use of an upper case letter for the first letter in the first word and lower case letters for all other words.

Uses temporarily relieves these symptoms of hay fever or other upper respiratory allergies, and common cold,

- headaches
- sneezing
- runny nose
- itchy watery eyes
- itching of the nose or throat
- nasal congestion
- fever
- minor aches and pains
- sinus congestion and pressure

Reviewer's Comments: The Electronic version places "hay fever..." before "the common cold." In the annotated Draft version. the Sponsor included as an additional use. This should be deleted. should be deleted form the indications unless there are clinical data to support use in this indication. The Labeling Rule requires vertical placement of bullets. The reviewers suggest that the order in which the indications are cited be revised to utilize available space.

Warnings

Alcohol warning: If you consume 3 or more alcoholic drinks daily, ask your doctor whether you should take acetaminophen or other pain relievers/fever reducers. Acetaminophen may cause liver damage.

Do not use if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.

Ask a doctor before use if you have

- heart disease
- high blood pressure
- thyroid disease
- diabetes
- glaucoma
- a breathing problem such as emphysema or chronic bronchitis
- trouble urinating due to an enlarged prostrate gland

Reviewer's Comments: The Electronic version lacked bulleting and the annotated Draft version, although bulleted, was not vertically bulleted. Sponsor should revise this section as shown above.

Ask a doctor or pharmacist before use if you are

- taking sedatives or tranquilizers

When using this product

- do not use more than directed
- avoid alcoholic drinks
- excitability may occur, especially in children
- be careful when driving a motor vehicle or operating machinery
- alcohol, sedatives, and tranquilizers may increase drowsiness

Reviewer's Comments: "Do not use more than directed" is to be bolded according to the citation in the CFR 341.80(c)(1)(i)(a). Sponsor incorrectly stated rather than and this warning should be placed under "Stop use and ask a doctor if". The reviewers suggest that the order in which the indications are cited be revised to utilize available space. The Electron version lacked bulleting and the annotated Draft version, although bulleted, was not appropriately aligned. The Sponsor should revise this section as shown above.

Drug Facts (continued)

Stop use and ask a doctor if
- symptoms continue or get worse
- new or unexpected symptoms occur
- nervousness, dizziness or sleeplessness occurs
- a fever that lasts for more than 3 days
- [redacted]

Reviewer's Comment: Sponsor should follow the above format. Both the Electronic version and the annotated Draft version included warnings that were inappropriate or outdated. The Electron version lacked bulleting and the annotated Draft version, although bulleted, was not appropriately aligned. The Sponsor should revise this section as shown above.

Directions
- adults and children 12 years of age and over: take 2 caplets every 6 hours as needed; not more than 8 caplets in 24 hours unless directed by a doctor
- children under 12 years of age: ask a doctor

Other information
- store at [redacted] 20°-25°C (68°-77°F)
- avoid excessive heat

Inactive Ingredients calcium sulfate, [redacted], glyceryl behenate, maltodextrin, methylcellulose, methylparaben, polyethylene glycol, [redacted] starch, silicon dioxide, sodium lauryl sulfate, titanium dioxide

B. BLISTER PACK:

Labeling contains the following:

Product Name:	**Tavist Allergy /Sinus/Headache**
Established Name & Dosage strength:	(acetaminophen 500 mg, clemastine fumarate 0.335mg (equivalent to 0.25 mg clemastine) and pseudoephedrine HCl 30 mg tablets)
Statement of Identity:	antihistamine/nasal decongestant/pain reliever
Manufacturer:	Manufacturer: Novartis Consumer Heath, Inc. Summit, NJ 07901-1312 Lot Number XXXXX Exp. Date XXXXX

Reviewer's Comments: We recommend the inclusion of the established name.

APPEARS THIS WAY
ON ORIGINAL

Recommendations:

1. This initial draft labeling review serves as guidance for the upcoming scheduled labeling day discussion. Further revision of this draft labeling may be necessary following the discussion.

2. Sponsor is to submit its specifications for labeling prior to issuance of any action letter regarding labeling.

3. HFD-570 to provide additional comment on the ——— seal found on the principal display panel.

/S/ 6/19/00
Bettie Ryland, IDS

/S/ 6/19/00
Daiva Shetty, M.D.

/S/ 6/19/00
Marina Chang, R.Ph.
Leader, Team 1

APPEARS THIS WAY
ON ORIGINAL

Attachment 1: Prototype Drug Facts labeling

APPEARS THIS WAY

CC:
HFD-560/Director
HFD-560/Deputy Director /S/ 6/26/00
HFD-560/MO
HFD-/560/Team 1 leader
HFD-560/IDS

APPEARS THIS WAY
ON ORIGINAL

Nomenclature Review

APPEARS THIS WAY
ON ORIGINAL

Hilfiker.

APR 27 2000

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: February 4, 2000	DUE DATE: June 1, 2000	OPDRA CONSULT#: 00-0050

TO: Robert J. Meyer, M.D.
Director, Division of Pulmonary and Allergy Drug Products
HFD-570

THROUGH: David Hilfiker, Project Manager
HFD-570

PRODUCT NAME: Tavist Allergy/Sinus/Headache Tablet (clemastine 0.25mg, pseudoephedrine HCl 30mg, and acetaminophen 500mg tablets) NDA #: 21-082	MANUFACTURER: Novartis Consumer Health, Inc. Summit, NJ 07901-1312

SAFETY EVALUATOR: Carol Pamer, R.Ph.

SUMMARY: In response to a consult from the Division of Pulmonary and Allergy Drug Products (HFD-570), OPDRA conducted a review of the proposed proprietary name "Tavist Allergy/Sinus/Headache" caplet to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: From a safety perspective, OPDRA does not object to the use of the name "Tavist Allergy/Sinus/Headache", but with reservation (see review). We have made recommendations for labeling revisions to minimize potential errors with the use of this product. See the checked box below.

☐ FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDAs from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

☒ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDAs from this date forward.

☐ FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDAs from this date forward.

/S/ 4/27/2000
Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 480-8173

/S/ - 4/27/00
Peter Honig, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Postmarketing Drug Risk Assessment (OPDRA)

HFD-400; Parklawn Building Room 15B-03

FDA Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: April 20, 2000

NDA NUMBER: 21-082

NAME OF DRUG: Tavist Allergy/Sinus/Headache Caplet,
(clemastine, pseudoephedrine HCl, and acetaminophen tablets)

NDA HOLDER: Novartis Consumer Health, Inc.
Summit, NJ 07901-1312

I. INTRODUCTION

This consult was written in response to a request from the Division of Pulmonary and Allergy Drug Products (HFD-570) for assessment of the proposed proprietary name "Tavist Allergy/Sinus/Headache" (TASH). TASH is a non-prescription drug product that contains clemastine fumarate equivalent to clemastine 0.25 mg, pseudoephedrine HCl 30 mg, and acetaminophen 500 mg per capsule-shaped tablet ("caplet"). The recommended dosing for adults and children 12 years of age and over is 2 caplets every 6 hours as needed, not to exceed 8 caplets in any 24-hour period, unless directed by a doctor. There is no dosing provided for children under 12 years of age; the consumer is instructed to consult a doctor. A statement entitled "Uses" is provided on the carton and reads as follows:

Uses temporarily relieves these symptoms of hay fever or other upper respiratory allergies, the common cold,
• sneezing • runny nose • itchy watery eyes • itching of the nose or throat • nasal congestion
• sinus congestion and pressure • headaches • minor aches and pains • fever

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[i,ii,iii] as well as several FDA databases[iv] for existing drug names which

[i] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).
[ii] American Drug index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.
[iii] Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

sound alike or look alike to "Tavist Allergy/Sinus/Headache" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[v].

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name "Tavist Allergy/Sinus/Headache". Potential concerns regarding drug marketing and promotion related to this proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

The Expert Panel noted that there are currently several "Tavist" brand products marketed in the U.S., with and without a prescription. Because of this, a high level of consumer confusion among the products seems likely. These products are listed below.

Tavist Allergy (Tablets)	**OTC: Tablets, clemastine 1 mg (base) (Formerly Tavist-1)**	**One tablet every 12 hours, not to exceed 2 tablets per 24-hour period**
Tavist	**Rx only: Tablets, clemastine 2 mg (base)**	**One tablet three times daily, not to exceed 3 tablets per 24-hour period**
Tavist	**Rx only: Syrup, clemastine 0.5mg per 5 mL**	**2 to 4 teaspoons twice daily, not to exceed 12 tsp/day (6mg clemastine) Children 6-12 y.o.: 1-2 tsp twice/day, not to exceed 6 tsp/day (3mg clemastine)**
Tavist-D Caplets Antihistamine/Nasal Decongestant	**OTC: Tablets, PPA 75mg, clemastine 1 mg. (Extended release PPA)**	**One tablet every 12 hours, not to exceed 2 tablets per 24-hour period**
Tavist-D Tablets	**OTC: Tablets, PPA 75mg, clemastine 1 mg. (Extended release PPA)**	**One tablet every 12 hours, not to exceed 2 tablets per 24-hour period**
Tavist Sinus (Caplets)	**OTC: "Caplets", APAP 500mg, pseudoephedrine HCl 30mg**	**Two tablets every 6 hours, not to exceed 8 per 24-hour period**
Tavist Sinus (Gelcaps)	**OTC: "Gelcaps", APAP 500mg, pseudoephedrine HCl 30mg**	**Two tablets every 6 hours, not to exceed 8 per 24-hour period**

In addition, a representative from DDMAC noted that the firm has encoded the FDA-approved indications, "allergy/sinus/headache", into the trade name for this product, which is a concern with reminder ads. However, this practice is widespread among OTC drug products. The regulation of promotion and advertising of OTC drug products currently falls under the jurisdiction of the Federal Trade Commission and not the FDA.

[iv] COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.
[v] WWW location http://www.uspto.gov/tmdb/index.html.

B. SAFETY EVALUATOR RISK ASSESSMENT

An OPDRA Expert Panel discussion was held to address the drug product name "Tavist Allergy/Sinus/Headache Caplet". Several other Tavist products are marketed in the U.S. We have concerns that this may provide a significant source of confusion and medication errors for consumers. However, the practice of using "family tradenames" in widespread in the OTC drug market. As an issue for future study, we have general concerns with the use of "family tradenames" in the U.S., as they likely contribute to considerable product confusion among consumers.

Some issues were also raised in the Expert Panel discussion by DDMAC concerning the proposed name and drug promotion and advertising. *Specifically, the sponsor has encoded the FDA-approved indications into the trade name.* However, FDA currently has no regulatory authority for OTC drug product advertising and promotion.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

We note that the term "caplet" is used on the front panel and in "DIRECTIONS" for this product. Although the term "caplet" has been used extensively in the OTC drug market, "caplet" is not an official USP dosage form. *We recommend that a footnote be added to the front panel in which the sponsor defines caplet as a "capsule-shaped tablet".*

IV. RECOMMENDATIONS

A. From a safety perspective, OPDRA does not object to the use of the proprietary name "Tavist Allergy/Sinus/Headache", but with reservation. As an issue for future study, we have general concerns with the use of "family tradenames" in the U.S., as they likely contribute to considerable product confusion among consumers.

OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated.

B. The term "caplet" should be defined for the consumer on the front panel of the product carton, to comply with official USP/NF dosage form designations.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Carol Pamer, R.Ph. at 301-827-3245.

/S/

Carol Pamer, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

/S/ 4/27/2000

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

APPEARS THIS WAY
ON ORIGINAL

cc: NDA 21-082
HFD-570; Division Files/David Hilfiker, Project Manager
HFD-570; Robert Meyer, Division Director
HFD-040, Patricia Staub, Senior Regulatory Review Officer, DDMAC
HFD-400; Carol Pamer, Safety Evaluator, OPDRA
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Director, OPDRA (electronic copy)

L:\OPDRA00\PAMER\000050TAVISTA-S-H.FIN.DOC

APPEARS THIS WAY
ON ORIGINAL

Patent Certification

In accordance with 314.50(i)(1)(ii), in the opinion and to the best knowledge of Novartis Consumer Health, Inc., there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

Signed: Date:

Vincent De Stefano
Associate Director, Regulatory Affairs
Novartis Consumer Health, Inc.

10/20/99

NEW DRUG APPLICATION

CLEMASTINE FUMARATE/ ACETAMINOPHEN/PSEUDOEPHEDRINE HYDROCHLORIDE TABLETS

PATENT INFORMATION

Pursuant to 21 CFR 314.53(c)(3), the applicant declares that it believes that there are no unexpired patents which claim the drug or the drug product or which claim a method of using the drug product and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

Signed Vincent DeStefano Date 10/7/99

Vincent De Stefano
Associate Director
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Patent Certification

Because the clinical studies conducted in support of this application were conducted by Novartis Consumer Health, Inc., this NDA is being filed under Section 505(b)(1) of the U.S. Food, Drug, and Cosmetic Act and, therefore, does not require patent certification. The applicant is not aware of any patents which claim the drug for which this NDA is being filed, or which claims a method of using such drug where a claim of patent infringement could reasonably be asserted against Novartis Consumer Health, Inc.

Signed: Date:

Vincent De Stefano 10/7/99

Vincent De Stefano
Associate Director, Regulatory Affairs
Novartis Consumer Health, Inc.

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 21-082 **SUPPL #** _____

Trade Name Tavist All/Sin/Head **Generic Name** clemastine/PSE/acet

Applicant Name Novartis Consumer Health **HFD-**570

Approval Date March 1, 2001

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 questions about the submission.

   a) Is it an original NDA? YES/ X / 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 / X / 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 /_X_/

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

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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 /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 # _____ _____

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 /_X_/ NO /___/

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

NDA # 17-661, 18-675 Tavist Tablets, Syrup

NDA # (OTC monograph) Theraflu Sinus

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. 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 /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 /_X_/ 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 9:**

_____

_____

(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 /_X_/

(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 /_X_/

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:

Investigation #1, Study # HSC-305

Investigation #2, Study # HSC-306

Investigation #3, Study # _____

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 /_X_/
Investigation #2	YES /___/	NO /_X_/
Investigation #3	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:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(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 /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(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"):

Investigation #_1_, Study # HSC-305

Investigation #_2_, Study # HSC-306

Investigation #__, Study # _____

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	
IND # _____ YES /_X_/	NO /___/ Explain: _____
	_____
	_____
Investigation #2	
IND # _____ YES /_X_/	NO /___/ 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 /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ 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 /_X_/

If yes, explain: _____

_____

_____

_____ _____

Signature of Preparer Date

Title:_____

_____ _____

Signature of Office of Division Director Date

cc:
Archival NDA
HFD-570/Division File
HFD-570/Hilfiker
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

APPEARS THIS WAY
ON ORIGINAL

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

/s/

David Hilfiker
3/1/01 05:28:23 PM

Robert Meyer
3/5/01 11:12:19 AM

NEW DRUG APPLICATION

CLEMASTINE FUMARATE/ ACETAMINOPHEN/PSEUDOEPHEDRINE HYDROCHLORIDE TABLETS

DEBARMENT CERTIFICATION STATEMENT

Novartis Consumer Health, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Signed Vincent De Stefano Date 10/7/99

Vincent De Stefano
Associate Director
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

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

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

NOVARTIS

NEW CORRESP
NC

May 30, 2000

ORIGINAL

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: Financial Disclosure Statement

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 a telephone conversation of May 17 with Linda Carter, Special Assistant to Director of Drug Evaluation I/Associate Director Office of Regulatory Affairs, during which time the Financial Disclosure Statement for the covered clinical studies HSC 305 and HSC 306 for this NDA was discussed. At the conclusion of our conversation, NCH agreed to submit a revised Certification Statement to the NDA that states that no outcome of payments were paid to the investigators(s), and that the investigator(s) had no proprietary interest in the tested product.

Included in this submission, is the signed and dated revised Certification Statement.

I can be reached at (908) 598-7821, if you have any questions.

Sincerely,

Novartis Consumer Health, Inc.

Nico C. Nicolaou
Manager, Regulatory Affairs

Enclosure
cc: Linda Carter, Special Assistant to Dir. of Drug Evaluation I/Assoc. Dir., Office of RA
Dave Hilfiker, Project Manager, Division of Pulmonary Drug Products

NEW DRUG APPLICATION

CLEMASTINE FUMARATE/ACETAMINOPHEN/PSEUDOEPHEDRINE HYDROCHLORIDE TABLETS

CERTIFICATION: FINANCIAL INTEREST AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

As the sponsor of the submitted studies (HSC 305 and HSC 306), I certify that, Novartis Consumer Health, Inc., has not entered into any financial arrangement(s) with the clinical investigator(s) of these studies, whereby the value of compensation to the investigator(s) could be affected by the outcome of the study (ies) as defined in 21 CFR 54.2(a), and that no such outcome of payments were paid to the investigator(s).

In addition, the investigator(s) had no proprietary interest(s) in the tested product as defined in 21 CFR 54.2(c), including but not limited to, a patent, trademark, copyright or licensing agreement.

Finally, I certify that this information is accurate and to the best of my knowledge.

Name: Russ Jones Title: Director, DRA

Signature:  Date: 5/30/00

APPEARS THIS WAY
ON ORIGINAL

Hilfiker

OCT 18 1999

NDA 21-082

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

Attention: Vincent De Stefano
Associate Director
Regulatory Affairs

Dear Mr. De Stefano:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Tavist Allergy/Sinus/Headache (0.335 mg clemastine fumarate/500 mg acetaminophen/30 mg pseudoephedrine hydrochloride) Tablets

Therapeutic Classification: Standard (S)

Date of Application: October 7, 1999

Date of Receipt: October 8, 1999

Our Reference Number: NDA 21-082

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on December 7, 1999, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be August 8, 2000, and the secondary user fee goal date will be October 8, 2000.

We acknowledge your submission of a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55. We will notify you within 120 days of receipt whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric

exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products, HFD-570
Attention: Division Document Room 10B-03
5600 Fishers Lane
Rockville, Maryland 20857

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

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

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

cc:
Archival NDA 21-082
HFD-570/Div. Files
HFD-570/Hilfiker
HFD-570/Schumaker/10-15-99
DISTRICT OFFICE

/S/ 10-15-99

Drafted by: HFD-570/Hilfiker/October 15, 1999
Final: HFD-570/Hilfiker/10-15-99
Filename: c:\my_documents\N21082\99-10-15.acltr.doc

ACKNOWLEDGEMENT (AC)

/S/

10/15/99.

3

APPEARS THIS WAY
ON ORIGINAL

Division Director's Memorandum (addendum)

Date: Tuesday, February 27, 2001
NDA: 21-082
Sponsor: Novartis
Proprietary Name: Tavist Allergy/Sinus/Headache Tablets
User Fee Due Date: March 8th, 2001 (for resubmission)

Introduction: This is resubmission to NDA 21-082for Tavist Allergy/Sinus/Headache tablets, which was not approved previously due to CMC concerns, including that the — manufacturer had not achieved a satisfactory GMP inspection prior to the last action.

Chemistry/Manufacturing and Controls: In addition to the — issues being resolved, the other CMC deficiencies were also resolved by the company within an additional cycle of review.

Pharm/Tox: No new issues were identified this cycle.

Biopharm: No additional issues this cycle.

Clinical / Statistical: No additional issues as this product was already deemed approvable (the sponsor met the concerns over the proposed —— dosing of clemastine, and has otherwise addressed the PK concerns of such a triple-combination preparation showing no interactions).

Labeling: The minor labeling comments in the last letter were satisfactorily answered and the labeling as finally proposed is acceptable from DPADP's standpoint (as well as DOTCDP's as per their review). Note that the CMC reviewers have recommended increased prominence to the admonition to protect from heat (i.e., bolded font), due to degradation concerns. The company has already printed some cartons, and therefore we will have them commit to a bolded statement on the heat issue by 6 months or the next printing, whichever is earlier.

Pediatrics: Given this is a fixed combination of common moieties where the acetaminophen dose is inappropriately high for those under 12, we will waive pediatric studies under the age of 12. There appears to be no significant health gain to the population for insisting on such studies, because products/dosage forms exist to address the symptoms targeted by this combination in younger patients.

Conclusions: This NDA, from DPADP's perspective, can be approved. This action will, of course, require DOTCDP concurrence and Dr. Ganley's sign off.

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

APPEARS THIS WAY
ON ORIGINAL

/s/

Robert Meyer
2/27/01 05:19:19 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

Division Director's Memorandum

Date:	Friday, July 28, 2000
NDA:	21-082
Sponsor:	Novartis
Proprietary Name:	Tavist Allergy/Sinus/Headache Tablets
User Fee Due Date:	August 8th, 2000 (ten month)

Introduction: This is new NDA by Novartis Consumer Health for a triple-combination of clemastine fumarate 0.335 mg, acetaminophen 500 mg, and pseudoephedrine HCL (PSE) 30 mg in a film-coated, capsule-shaped tablet. The proposed dose is up to 2 tablets every 6 hours in patients ages 12 and above. While such an application of a combination product might ordinarily be based on a PK program, the particular dosing of clemastine proposed in this immediate-release product (0.5 mg of the base QID) is different from that approved (1 mg BID). Therefore, in addition to a PK approach to assure the acceptability of the PSE and acetaminophen and the combination product, there were clinical studies done to assure that the efficacy and safety of clemastine was acceptable despite the changed dosing quantity and frequency.

Chemistry/Manufacturing and Controls: While many of the CMC issues have been adequately addressed, there are remaining issues that preclude approval this cycle. Most notable is that the site where [redacted] is manufactured has GMP violations that need correction and re-inspection prior to [redacted] being acceptable for use in an approved product. The other issues are less substantive and should be resolvable by the company within an additional cycle of review.

Pharm/Tox: No new new issues were identified.

Biopharm: See Dr. Wakelkamp-Barnes' review for details. Essentially, the sponsor did show that their triple combination tablet provided bioequivalent exposure to PSE and acetaminophen as that from the approved TheraFlu Sinus tablets (a combination of PSE and acetominophen). Studies also confirmed that the formulation and other components did not alter the biopharmaceutics of the clemastine. Therefore, from the standpoint of pharmacokinetics, the sponsor successfully addressed the biopharmaceutics issues related to such a product.

Clinical / Statistical: See Dr. Lee's primary review and Dr. Elashoff's statistical review for details. The sponsor performed two clinical studies to address the safety and efficacy concerns related to clemastine at this dose and frequency. One was a multiple dose efficacy and safety study (305) and the other a single, day-in-the-park study primarily to define efficacy. Study 305 compared the efficacy of clemastine at 0.5 mg every 6 hours to clemastine dosed 1.0 mg every 12 hours to placebo in the treatment of SAR symptoms. Essentially, this study showed comparable efficacy for the two dosing regimens. The safety profile, while not greatly different between the two, frequently favored the 0.5 mg QID dosing. Study 306 compared TheraFlu (i.e., PSE and acetaminophen) to the proposed triple combination product and placebo in the treatment of symptoms of SAR (to assure that this dose of clemastine meaningfully adds to the other two monograph drugs in this triple combination product for the treatment of SAR). This study confirmed

efficacy of the triple-combination product, but not for TheraFlu, in the day-in-the-park study. The onset of effect was seen by 2 hours and lasted throughout the 6 hour dosing interval.

From the clinical standpoint, this product should be approvable, as the sponsor has met the concerns over the proposed altered dosing of clemastine, and has otherwise addressed the PK concerns of such a triple-combination preparation (showing no interactions).

Labeling: This being a proposed OTC product, the labeling review was done by the OTC division and labeling comments will be forwarded to the sponsor in the action letter (since this cycle will not be an approval). A concern raised by Dr. Lee was the a claim of ——— This seems inappropriate given the —, observed in study 306 and the implied comparative nature of such a statement.

Conclusions: This NDA is approvable, pending resolution of the CMC issues and the revision of the proposed labeling. As stated above, the major issue to resolve is the acceptability of —— manufacturing site, which according to internal discussions is not likely to be addressed for many months (i.e., beyond the 12-month User Fee Goal date). Therefore, it appears most reasonable to take an action on this application (approvable) and allow the sponsor to fully respond when all issues are resolved.

/S/

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

cc: ORIG NDA 21-022
HFD-570/DIV FILE
570/ HILFIKER
570/ MEYER

APPEARS THIS WAY
ON ORIGINAL

Hilfiker

MEDICAL TEAM LEADER MEMORANDUM

DATE: July 7 2000

TO: NDA 21-082
/S/

FROM: Badrul A. Chowdhury, MD, PhD
Acting Team Leader, Division of Pulmonary and Allergy Drug Products
/S/ 7/7/00

SUBJECT: Secondary medical review of Tavist® Allergy/Sinus/Headache Tablets NDA

CC: HFD-570: Meyer, Lee, Elashoff, Wakelkamp, HILFIKER
HFD-560: Ganley, Shetty, Chang, MERRITT

Administrative

NDA 21-082 was submitted by Novartis Consumer Health on October 7, 1999. The user fee goal date for action on this application is August 6, 2000. This drug product is a combination of clemastine fumerate 0.335 mg (clemastine base 0.25 mg), acetaminophen 500 mg, and pseudoephedrine hydrochloride 30 mg in a film coated tablet (Clemastine Triple Combination, CTC). The proposed trade name is Tavist® Allergy/Sinus/Headache. OPDRA does not have an objection this name. The proposed dose for adults and children down to 12 years is 2 tablets every 6 hours as needed. The proposed indications are temporary relief of ——— symptoms of hay fever or other upper respiratory allergies, common cold, and ———. The sponsor intends to market this drug product for nonprescription over-the-counter (OTC) sale.

Clemastine is a first generation H1 receptor antagonist, acetaminophen is an analgesic and antipyretic, and pseudoephedrine is a decongestant. Acetaminophen and pseudoephedrine immediate release formulations are approved OTC monograph ingredients for cough, cold, and allergy symptoms (21 CFR 341). Acetaminophen is allowed at 1000 mg every 6 hours in adults and children down to 12 years. Pseudoephedrine is allowed at 60 mg every 4-6 hours in adults and children down to 12 years. Both of these ingredients are within these allowed ranges in the CTC formulation. Clemastine is not a monograph product. Clemastine 1 mg (Tavist-1) is currently marketed by Novartis Consumer Health as an OTC product (NDA 20-925). The recommended dose is one tablet every 12 hours. Clemastine has not been approved for use at a frequency less than every 12 hours in any other product. Since clemastine is not a monograph antihistamine, and is not approved by dosing every 6 hours, the proposed combination drug product requires FDA approval before marketing. As agreed upon on the December 9, 1996, pre-NDA meeting, for approval of this combination product the sponsor is required to demonstrate the absence of a pharmacokinetic interaction among the components, and to demonstrate that the clemastine 0.5 mg every 6 hours is effective and has a safety profile comparable to that of clemastine at the approved OTC dose of 1 mg every 12 hours.

Chemistry and Manufacturing

The proposed drug product is a single layer, immediate release, capsule-shaped, film-coated tablet that contains 0.25 mg clemastine, 500 mg acetaminophen, and 30 mg pseudoephedrine. The tablet is white and is debossed with "Tavist" on one side and "C-A-S" on the other side. There are multiple CMC deficiencies that may prevent approval of this product. The DMF of some components of the product is not complete, and the supplier of ———— has failed the Agency's compliance inspection.

Pharmacology and toxicology

No new preclinical studies were submitted with this application. There are no outstanding pharmacology and toxicology issues in this submission.

Clinical studies

The sponsor has submitted four pharmacokinetic studies, two pharmacodynamic studies, one multi-dose efficacy and safety study, and one day-in-the park efficacy and safety study. Biopharmaceutics reviewer Dr. Wakelkamp reviewed the pharmacokinetic studies (HSC-151, HSC-152, HSC-153B, HSC-302) and has concluded that there are no pharmacokinetic interactions among the components. These studies are not further commented upon in this memorandum. The pharmacodynamic study HSC-303 assessed the skin test suppression after single dose of clemastine, and the pharmacodynamic study HSC-304 assessed nasal secretion and symptoms after nasal allergen challenge in patients pre-treated with single dose of clemastine. The pharmacodynamic studies are supportive and are not reviewed in this memorandum. The multi-dose and the day-in-the park clinical studies (HSC-305, HSC-306) are important for this application and are briefly reviewed in the subsequent sections. Study HSC-305 was conducted to demonstrate that clemastine 0.5 mg every 6 hours is safe and effective as compared to the currently available 1 mg dose given every 12 hours. Study HSC-306 was conducted to demonstrate that CTC in a QID dosage form is safe and effective, and the triple combination of clemastine, acetaminophen, and pseudoephedrine provides added benefit over the double combination of acetaminophen, and pseudoephedrine. Detail review of the sponsor's submission can be found in Dr. Lee's medical review and Ms. Elashoff's biostatistics review.

Data integrity in the clinical studies was verified by analyses of the electronic data set by biostatistics reviewer, and by DSI audit of two sites based on their contribution to the clinical program. No deficiency during the DSI audit was noted.

HSC-305: Multi-dose efficacy and safety study

This was a three-arm, 1:1:1 randomized, multicenter, double-blind, double-dummy, placebo controlled, parallel-group study that evaluated efficacy and safety of clemastine 0.5 mg QID versus clemastine 1.0 mg BID versus placebo for allergy symptom relief. The study enrolled 12 to 67 year old (overall mean age 33 year) patients with seasonal allergic rhinitis (SAR) in 12 US centers during the fall allergy season of 1995. Eligible patients were randomized to clemastine 0.5 mg QID, clemastine 1 mg BID, or placebo for a 2-week double-blind treatment period. Since the study employed a double-dummy design, all patients took study medications four times daily, within an hour of 6 AM, 12 noon, 6 PM, and 12 midnight. Efficacy assessment was primarily based on patient scoring of severity of four nasal

symptoms (nasal discharge, nasal congestion, nasal itching, and sneezing) and four non-nasal symptoms (itchy eyes, tearing, redness of eyes, and itchy ears and palate) on a 0-6 scale. Scoring was done before the 12 noon dose reflecting how they felt in the previous 24 hours (reflective) and at the time of scoring (instantaneous). The protocol stated that the primary efficacy variables were to be nasal discharge, and sneezing scored by the investigator.

A total of 412 patients were randomized, 140 to placebo, 137 to clemastine 0.5 mg QID, and 140 to clemastine 1.0 mg BID. About 90% of randomized patients completed the study. Mean number of days study medication was taken ranged from 13.2 to 13.6 for the three treatment groups, and mean number of dose taken per day was 3.9 for all groups. The protocol did not specify the time point (day), dose comparison, or score (one symptom, or composite) for efficacy assessment. Results of investigator assessed nasal discharge and sneezing scores (primary efficacy variable as stated in the protocol), and patient assessed scores for the same variables are shown in Table 1 and Table 2. Overall, both doses of clemastine were better than placebo. Lack of statistical significance at later time points was due to placebo response rather than any evident regression in the active treatment group. Biostatistics reviewer Ms. Elashoff also analyzed the mean change from baseline total symptom score using the reflective and instantaneous scores from patient diary. Patient recording of instantaneous score is DPADP's preferred method of evaluating efficacy of allergic rhinitis drugs. Results based on this analysis are shown in Table 3. This analysis also supports efficacy of both doses of clemastine. Safety of clemastine 0.5 mg QID was assessed by recording of adverse events, physical examination, clinical chemistry, and hematology. Results supports safety of clemastine 0.5 mg QID. Common adverse events occurring in clemastine treated patients more frequently than placebo were somnolence, fatigue, and dry mouth.

Table 1. Mean change from baseline in investigator assessed symptom score*

	Placebo	Clem 0.5 QID	Clem 1.0 BID	p-value, placebo vs	
				Clem 0.5 QID	Clem 1.0 BID
Nasal discharge					
Baseline	4.27 (138)	4.33 (136)	4.31 (134)		
Day 4	0.70 (138)	1.49 (134)	1.53 (133)	[redacted]<0.001	[redacted]<0.001
Day 8	1.03 (134)	1.45 (132)	1.51 (129)	[redacted]0.022	[redacted]0.002
Day 15	1.52 (123)	1.61 (127)	1.73 (129)	0.657	0.288
Sneezing					
Baseline	3.97 (138)	3.90 (136)	3.91 (134)		
Day 4	0.85 (138)	1.85 (134)	1.90 (133)	[redacted]<0.001	[redacted]<0.001
Day 8	1.21 (134)	1.91 (132)	1.60 (129)	[redacted]<0.001	[redacted]0.028
Day 15	1.65 (123)	2.01 (127)	1.94 (129)	[redacted]0.050	[redacted]0.141

* Symptoms scored on 0-6 scale. Results expressed as mean (n)

APPEARS THIS WAY ON ORIGINAL

Table 2. Mean change from baseline in patient assessed symptom score*

	Placebo	Clem 0.5 QID	Clem 1.0 BID	p-value, placebo vs	
				Clem 0.5 QID	Clem 1.0 BID
Nasal discharge (Reflective)					
Baseline	4.25 (138)	4.36 (135)	4.24 (134)		
Day 4	0.79 (138)	1.40 (135)	1.32 (133)	[redacted]<0.001	[redacted]<0.001

APPEARS THIS WAY ON ORIGINAL

	Placebo	Clem 0.5 QID	Clem 1.0 BID	p-value, placebo vs	
				Clem 0.5 QID	Clem 1.0 BID
Day 8	1.08 (132)	1.60 (131)	1.48 (131)	[redacted]	[redacted]
Day 15	1.38 (123)	1.64 (126)	1.63 (128)	0.149	0.126
Sneezing (Reflective)					
Baseline	4.02 (138)	3.92 (135)	3.89 (134)		
Day 4	0.91 (138)	1.67 (135)	1.62 (133)	[redacted]	[redacted]
Day 8	1.19 (132)	1.96 (131)	1.70 (131)	[redacted]	[redacted]
Day 15	1.46 (123)	2.14 (126)	1.78 (128)	[redacted]	0.059
Nasal discharge (Instantaneous)					
Baseline	3.49 (138)	3.52 (135)	3.46 (134)		
Day 4	0.45 (138)	0.97 (135)	1.01 (133)	[redacted]	[redacted]
Day 8	0.67 (132)	1.07 (131)	1.14 (131)	0.066	[redacted]
Day 15	0.98 (123)	1.07 (126)	1.20 (128)	0.861	0.254
Sneezing (Instantaneous)					
Baseline	2.89 (138)	2.74 (135)	4.24 (134)		
Day 4	0.33 (138)	0.96 (135)	1.07 (133)	[redacted]	[redacted]
Day 8	0.57 (132)	1.10 (131)	1.02 (131)	[redacted]	[redacted]
Day 15	0.81 (123)	1.16 (126)	1.10 (128)	0.188	0.272

* Symptoms scored on 0-6 scale. Results expressed as mean (n)

Table 3. Mean change from baseline in patient assessed sum of all symptom scores*

	Placebo	Clem 0.5 QID	Clem 1.0 BID	p-value, placebo vs	
				Clem 0.5 QID	Clem 1.0 BID
Reflective					
Wk 1 change	6.0 (139)	10.0 (135)	9.6 (134)	ND	ND
Wk 2 change	9.4 (128)	11.9 (128)	11.4 (129)	ND	ND
Wk 1&2 change	7.7 (139)	11.1 (135)	10.5 (134)	ND	ND
Instantaneous					
Wk 1 change	3.6 (139)	6.9 (135)	7.3 (133)	[redacted]	[redacted]
Wk 2 change	6.4 (128)	8.5 (128)	8.7 (129)	0.0616	[redacted]
Wk 1&2 change	5.0 (139)	7.7 (135)	8.0 (133)	[redacted]	[redacted]

* Symptoms scored on 0-6 scale. Total of 8 symptoms. Score range 0-48. Results expressed as mean (n)

HSC-306: Day-in-the park efficacy and safety study

This was a three-arm, 2:2:1 (drug:drug:placebo) randomized, double-blind, placebo controlled, one-day park study that evaluated efficacy and safety of the CTC triple combination versus TheraFlu (TF) Sinus tablets (pseudoephedrine 30 mg, and acetaminophen 500 mg) versus placebo for allergy symptom relief. The primary comparison was between the CTC and TF sinus groups. The placebo group was added to validate the clinical model. The study enrolled 12 to 62 year old (overall mean age about 28 year) patients with seasonal allergic rhinitis (SAR) in two US centers located in California and Nebraska during the fall allergy season of 1997. Patients were screened within 4 weeks of the study. During the screening period patients recorded their rhinitis symptoms, and were required to have a score above a pre-specified cutoff for inclusion in the study. Eligible patients were randomized to CTC, TF Sinus, or placebo arm. Study drug was administered at about 9 AM and at 3 PM while the patients were in a designated outdoor park. Patients scored symptoms 90, 60, and 30 minutes before dosing, 30 minutes after the dosing, and

hourly thereafter till 5 PM when they left the park. Four more hourly scores starting at 6 PM were recorded at home. Patients returned to the investigator the day after to return their symptom scores from the previous night, and reported adverse events.

Symptoms scored by patients were stuffy nose (0-5 scale); nose blows and sneezing (0-8 scale); itchy nose, runny nose, sniffles, postnasal drip, watery eyes, itchy eyes/ears, itchy throat, cough, and headache (0-5 scale). Primary efficacy variable was "major symptom complex," defined as the sum of sneezing, itchy nose, runny nose, watery eyes, itchy eyes/ears, and itchy throat. These are typical histamine mediated symptoms.

A total of 298 patients were randomized, 61 to placebo, 119 to TF Sinus, and 118 to CTC. All patients except 4 completed the study. None used concomitant antihistamines during the study. Baseline symptom scores were comparable among the groups. Results of patient assessed "major symptom complex" (primary efficacy variable as stated in the protocol) is shown in Table 4. The study demonstrated statistically significant difference between the CTC and TF sinus group (primary comparison), and CTC and placebo group. As expected, TF sinus and placebo had about the same effect on this score. Onset of action based on major symptom complex for the CTC group compared to the placebo group was 2 hours, and efficacy was maintained at the end of dosing interval at 6 hours.

In this study safety was assessed by recording of adverse events. Common adverse events occurring in CTC group treated patients and more frequently than TF sinus and placebo groups were somnolence, and fatigue. These adverse events can be attributed to known sedative property of clemastine.

Table 4. Mean change from baseline in major symptom complex score*

	Placebo (n = 61)	TF sinus (n = 119)	CTC (n = 118)	p-value		
				CTC vs TF	CTC vs Pbo	TF vs Pbo
Baseline	13.02	14.03	12.74			
Absolute change	4.90	4.88	6.61	0.002	0.023	0.720
Percentage change	36.38 %	34.23	50.02			

* Symptoms included were sneezing, itchy nose, runny nose, watery eyes, itchy eyes/ears, and itchy throat.

Efficacy assessment

Acetaminophen and pseudoephedrine are OTC monograph ingredients approved for use in drug products for cough, cold, and allergy symptoms (21 CFR 341). Clemastine is not listed in the OTC monograph and is not approved at the proposed 0.5 mg QID schedule as proposed for the CTC product. Therefore, for approval of this combination product from an efficacy standpoint the sponsor needs to demonstrate the absence of a pharmacokinetic interaction among the components, and efficacy of clemastine at a dose of 0.5 mg QID. The pharmacokinetic studies (HSC-151, HSC-152, HSC-153B, and HSC-302) show that there are no interactions among the components. The pharmacodynamic studies (HSC-303, and HSC-304) and the two clinical studies (HSC-305, and HSC-306) also support this conclusion. Efficacy of clemastine at a dose of 0.5 mg QID is supported by the multi-dose 2-week study HSC-305. Day-in-the park study HSC-306 further supports efficacy for the CTC product.

This study also supports the requirement that applies to prescription drug combination (21 CFR 300.50). This study demonstrated that addition of clemastine to the combination of acetaminophen and pseudoephedrine (CTC vs TF sinus) made a positive contribution to the claimed effects of the components.

Safety assessment

The sponsor submitted various types of data to support safety of the CTC combination product. Primary source of safety data is from the pivotal study multi-dose study HSC-305. Supplemental sources of safety data are from the day-in-the park study HSC-306, pharmacokinetic studies, pharmacokinetic studies, review of literature, and summary of postmarketing experience. Review of these data does not suggest that the combination product has any safety concerns. Most of the common adverse events, such as somnolence, fatigue, dry mouth, reported by the patients are due to known sedative and anticholinergic property of clemastine. No clinically meaningful changes in physical examination, laboratory values, or ECG were seen. A curious exception was elevation of plasma CPK levels seen in some patients. Four patients had large CPK elevation on treatment (125 to 1049, 158 to 1259, 85 to 1226, and 177 to 1700). All were from clemastine groups. Two patients were from study HSC-305 that had placebo comparator arm, and two patients were from studies that had no placebo arms (HSC-302, and HSC-151). Mean change of CPK, and shift table analyses do not show any meaningful changes between treatment and placebo arms. These are detailed in Dr. Lee's Integrated Summary of Safety. There is no plausible explanation for these elevations.

Recommendation

From a clinical standpoint this application is recommend an APPROVABLE action, or an APPROVAL action if the following issues are resolved prior to the action due date. However, from CMC standpoint this product may not approvable because of problems discussed above under the Chemistry and Manufacturing section.

The sponsor has satisfied the scientific rationale and regulatory requirement of this triple combination product for use in hay fever or other upper airway allergies, and common cold. However, use of this product for ——— is not supported by the submitted studies. Further, none of the ingredients on this combination product is approved OTC mongraph ingredients for ——— (21 CFR 341). Unless otherwise supported, the ——— claim should be removed the "uses" section of the label printed on the principal display panel of the cartoon.

The "seal" containing the statement '——————— on the principal display panel of the carton (label) implies that this product is superior to other similar products, or other similar products are ——————— Unless otherwise supported, this seal with the contained ' ——————— ' statement should be removed. Likewise, the ——————— statement on the front of the package implies a ——————— of action, and superiority to other similar products. Unless otherwise supported, this statement should be modified to remove the qualifier ———

Drowsiness and sedation was a commonly reported adverse event for this combination product. This adverse event should be prominently displayed in the label.

/s/

Charles Lee
2/16/01 02:59:28 PM
MEDICAL OFFICER

Mary Purucker
2/24/01 08:53:46 PM
MEDICAL OFFICER

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: N 021082

Trade Name: Tavist Allergy/Sinus/Headache

Generic Name: clemastine fumarate/pseudoephedrine sulfate/acetaminophen

Supplement Number. 000 **Supplement Type:** N

Dosage Form: caplet

Regulatory Action: AP **Action Date:** pending

COMIS Indication: TREATMENT OF [redacted] /NASAL CONGESTION/RUNNY NOSE/SNEEZING DUE TO COMMON COLD/MINOR ACHES AND PAIN RELIEF ASSOCIATED WITH COLD

Indication #1: treatment of symptoms of [redacted] hay fever, and common cold

Label Adequacy: Adequate for all pediatric age groups

Formulation Needed: No new formulation is needed

Comments (if any) This dosage form ("caplet") would be applicable to some pediatric age groups, but doses would need to be adjusted. The sponsor has requested a waiver from studying this combination in pediatric age ranges, and the Division has determined that a waiver is appropriate due mainly to safety concerns with the applicable dose of acetaminophen in children under 12 years of age.

Lower Range	Upper Range	Status	Date
0 years	12 years	Waived	3/8/01

Comments: Sponsor's reasons for waiver request for patients under 12 years of age: (1) product does not represent any clinical advantage to the products already on the OTC market; (2) one of the active ingredients, clemastine, has not been studied in patients under 12 years of age.

Division's reasons for granting a waiver were mainly that the use of this product under 12 years is not recommended due to safety concerns of the dose of acetaminophen that is directed. DH, 2-23-01

This page was last edited on 2/23/01

Signature /S/ Date 2/23/01

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **NDA 21082/000**
Stamp: **08-OCT-1999** Regulatory Due: **08-MAR-2001**
Applicant: **NOVARTIS CONS**
560 MORRIS AVE BLDG F
SUMMIT, NJ 079011312

Priority: **4S** Org Code: **570**
Action Goal: District Goal: **07-JAN-2001**
Brand Name: **TAVIST(ACETAMINOPHEN/CLEMASTINE FUMARATE**
Established Name:
Generic Name: **ACETAMINOPHEN/CLEMASTINE FUMARATE/PSEUDO**
Dosage Form: **TAB (TABLET)**
Strength: **0.335/ — /30.0 MG/TAB**

FDA Contacts: **D. HILFIKER (HFD-570) 301-827-1050 , Project Manager**
K. SWISS , Review Chemist
G. POOCHIKIAN (HFD-570) 301-827-1050 , Team Leader

Overall Recommendation:

ACCEPTABLE on 02-JAN-2001 by J. D AMBROGIO (HFD-324) 301-827-0062
WITHHOLD on 14-JUN-2000 by P. ALCOCK (HFD-324) 301-827-0062

Establishment: [redacted]
DMF No: —
AADA No:

Profile: CSN OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **02-NOV-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: [redacted]

Establishment: [redacted]
DMF No: —
AADA No:

Profile: CSN OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **08-MAY-2000**
Decision: **WITHHOLD**
Reason: ———————
Responsibilities: [redacted]

Establishment: **1911445**
NOVARTIS CONSUMER HEALTH INC
NORTHEAST US 6 AND INTERSTATE
LINCOLN, NE 68517
DMF No: ———
AADA No:

Profile: **TCT** OAI Status: **NONE**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Last Milestone: **OC RECOMMENDATION**
Milestone Date: **08-NOV-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**
FINISHED DOSAGE RELEASE TESTER

Establishment: **9611204**
NOVARTIS PHARMA INC (SANDOZ)
LICHSTRASSE 35
KLYBECK, BASEL, SZ 4002

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **02-JAN-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment: [redacted]

DMF No: —
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **21-DEC-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: [redacted]

APPEARS THIS WAY
ON ORIGINAL