CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-082

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-082

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/30 mg pseudoephedrine sulfate/500 mg acetaminophen) Tablets.

We acknowledge receipt of your submissions dated October 20, 1999, and March 1, 10, and 31, May 3, 8, and 18, June 14 and 15, September 7, October 30 and November 9, 2000, and January 2 and 15, February 1, 14, 22, and 23, 2001. Your submission of September 7, 2000, constituted a complete response to our August 4, 2000, action letter.

This new drug application provides for the use of Tavist Allergy/Sinus/Headache (clemastine fumarate/pseudoephedrine sulfate/acetaminophen) Tablets for temporary relief of symptoms associated with hay fever, allergic rhinitis, and the common cold.

We have completed the review of this application, as amended, and it is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the labeling for the blister submitted on September 7, 2000, and the immediate carton submitted on November 9, 2000 (24- count and 48-count carton presentations). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-082." Approval of this submission by FDA is not required before the labeling is used.

As agreed in your amendment of February 23, 2001, bold the statement, "Avoid excessive heat," found

in the carton labeling under *OTHER INFORMATION*, prior to the next printing or within 6 months, whichever comes first.

We remind you of your postmarketing study commitment in your submission dated February 1, 2001. This commitment is described below.

> Development, validation, and submission in a prior approval supplement, of a new method for estimation of chromatographic impurities in the drug substance, clemastine fumarate.
>
> Final Report Submission: On or before June 30, 2001

Submit chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of this commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to this postmarketing study commitment must be prominently labeled "Postmarketing Study Final Report" or "Postmarketing Study Correspondence."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

In line with Center for Drug Evaluation and Research policy, oversight of this application is being transferred to the Division of Over-the-Counter Drug Products. If you have any questions, contact Ms. Babette Merritt, Project Manager, at (301) 827-2222.

Sincerely yours,

/S/

Charles Ganley, M.D.
Director
Division of Over-The-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

/S/

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

/s/

Mary Purucker
3/1/01 01:43:26 PM
for R. Meyer

Charles Ganley
3/1/01 04:49:20 PM

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-082

APPROVABLE LETTER

Hilchlex

NDA 21-082

AUG 4 2000

Novartis Consumer Health, Inc.
560 Morris Avenue
Summit, NJ 07907-1312

Attention: Nico C. 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 acknowledge receipt of your submissions dated October 20, 1999, and March 1, 10, and 31, May 3, 8, and 18, and June 14 and 15, 2000.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following deficiencies.

1. Provide a suitable [redacted] method [redacted] for determination of clemastine fumarate drug substance-related impurities. [redacted]

2. [redacted]

3. The following comments pertain to the regulatory specifications of the drug product and are based on the data that have been provided.

[redacted]

WITHHOLD 1 PAGE (S)

a. [redacted]

b. [redacted]

6. The following comments pertain to drug product stability.

   a. Provide updated drug product stability data for all batches used in stability studies.

   b. Provide an updated stability protocol, including timepoints and stability indicating tests.

   c. Comments on the acceptance criteria and expiry period proposal for drug product stability batches will be withheld until a sufficient body of data for both blister presentations (including that specified in comment 3 above) is collected and submitted to the NDA. A single expiry period shall be issued for both drug product presentations.

   d. Provide the method that determines the number of batches to be placed on stability per year.

[redacted]

8. Based on the dissolution data for the batch that was used in the comparative bioavailability studies and other submitted stability data, revise the dissolution specifications to Q = — at 30 minutes for clemastine fumarate, pseudoephedrine hydrochloride, and acetaminophen.

During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the inspector. Satisfactory inspections will be required before this application may be approved.

In addition, it will be necessary for you to submit draft labeling revised as follows.

9. Add a footnote to the front panel of the carton label that defines caplet as a "capsule-shaped tablet."

10. The seal with the statement ———— on the front panel should be removed.

11. The statement, ———— located on the front panel, should be removed.

12. Revise the carton and blister labels according to the attached prototype labeling.

Further labeling recommendations may be forthcoming once the above deficiencies have been addressed.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

You are advised to contact the Division regarding the extent and format of your safety update prior to responding to this letter.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely yours,

/S/

Charles Ganley, M.D.
Director
Division of Over-The-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

/S/

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

Enclosure

PROTOTYPE LABELING (with FDA revisions)

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 / Fever Reducer
ALLERGY/SINUS/HEADACHE

Caplet (photo)
24 **CAPLETS**

FRONT PANEL

Antihistamine / Nasal Decongestant / Pain Reliever / Fever Reducer

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

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

- Itchy throat

Caplet (photo)

24 **CAPLETS***
* capsule-shaped tablet

BACK, BOTTOM, AND LEFT SIDE PANELS*

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:

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

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
- using another product containing acetaminophen, clemastine fumarate or pseudoephedrine HCl
- under a doctor's care for any continuing medical condition
- taking other drugs on a regular basis

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

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.

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

* Follow this DRUG FACTS label in content only. Font sizes for title, headings, subheadings, condensed test, and other graphical features must be in accordance with the regulations under 21 CFR 201.66.

RIGHT SIDE PANEL

UPC
Lot:
Exp.

BLISTER PACK

Tavist Allergy/Sinus/Headache
(clemastine fumarate 0.335 mg (equivalent to 0.25 mg clemastine), pseudoephedrine HCl 30 mg, and acetaminophen 500 mg tablets)
antihistamine/nasal decongestant/pain reliever/fever reducer

Manufacturer:	Novartis Consumer Health, Inc. Summit, NJ 07901-1312
Lot Number	XXXXX
Exp. Date	XXXXX

cc:
Archival NDA 21-082
HFD-570/Div. Files
HFD-570/Hilfiker
HFD-570/Lee/7-28-00
HFD-570/Chowdhury/7-28-00 /S/ 7/31/00
HFD-570/Wakelkamp/7-27-00
HFD-570/Uppoor/7-27-00
HFD-570/Huff /S/ 7/31/00
HFD-570/Swiss/7-27-00
HFD-570/Poochikian/7-27-00
HFD-570/Elashoff /S/ 7/31/00
HFD-570/Wilson /S/ 7/31/00
HFD-570/Meyer/7-28-00 /S/ 7/28/00
HFD-002/ORM
HFD-102/ADRA
HFD-42/DDMAC (with labeling) /S/ 7/31/00
HFD-560/OTC/Merritt (with labeling)/7-27-00
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: HFD-570/Hilfiker/July 24, 2000
Initialed by: HFD-560/Ryland
HFD-560/Shetty 8/4/00
HFD-560/Chang/7-27-00 /S/
HFD-560/Ganley
HFD-570/Barnes
Final: HFD-570/Hilfiker/7-28-00
Filename: c:\my_documents\N21082\000724aeltr

APPROVABLE (AE)

APPEARS THIS WAY
ON ORIGINAL