CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-150

APPROVAL LETTER

NDA 21-150

Pfizer Pharmaceuticals
Pfizer, Inc.
235 East 42nd Street
New York, NY 10017

Attention: John Tomaszewski, M.S.
Director, Regulatory Affairs

Dear Mr. Tomaszewski:

Please refer to your new drug application (NDA) dated January 18, 2000, received January 19, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyrtec-D 12 Hour (cetirizine hydrochloride 5 mg and pseudoephedrine hydrochloride 120 mg) Extended Release Tablets.

We acknowledge receipt of your submissions dated April 7, May 12, June 5, August 16, September 29, October 11 and 17, November 21 and 29, December 12 and 27, 2000, and January 17 and 18, February 12, 15, 20, and 28, March 27 and 28, April 23 and 27, July 26, and August 7, 2001. We further acknowledge receipt of your correspondence dated July 26, 2001. Your submission of February 12, 2001, constituted a complete response to our January 17, 2001, action letter.

This new drug application provides for the use of Zyrtec-D 12 Hour (cetirizine hydrochloride 5 mg and pseudoephedrine hydrochloride 120 mg) Extended Release Tablets for the relief of nasal and non-nasal symptoms associated with seasonal or perennial allergic rhinitis in adults and children 12 years of age and older.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the package insert, immediate container and carton labels submitted July 26, 2001. 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 21-150." Approval of this submission by FDA is not required before the labeling is used.

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.

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). You have fulfilled the pediatric study requirement at this time for pediatric patients 12 years of age and older. A waiver for pediatric studies for patients below 12 years of age is granted at this time for this action.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

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

If you have any questions, call Dr. Craig Ostroff, Regulatory Management Officer, at 301-827-5585.

Sincerely,

{See appended electronic signature page}

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Marianne Mann
8/10/01 10:55:29 AM
Dr. Mann is signing as Acting Director in the absence of Dr. Meyer, th
e Division Director.

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-150

APPROVABLE LETTER

APPROVABLE LETTER

January 17 2001

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-150

Pfizer Pharmaceuticals
Pfizer, Inc.
235 East 42nd Street
New York, NY 10017

Attention: John Tomaszewski
Director, Regulatory Affairs

Dear Mr. Tomaszewski:

Please refer to your new drug application (NDA) dated January 18, 2000, received January 19, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyrtec-D 12 Hour (cetirizine hydrochloride 5 mg and pseudoephedrine hydrochloride 120 mg) Extended Release Tablets.

We acknowledge receipt of your submissions dated April 7, May 12, June 5, August 16, September 29, October 11 and 17, November 21 and 29, and December 12 and 27, 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, which are cross-referenced (in parentheses) to previous comments stated in our letter to your firm dated July 28, 2000.

The following comments pertain to the drug substance:

1. Tighten the acceptance criterion for individual impurities in the cetirizine hydrochloride drug substance to <0.1%. (comment 1)

2. Establish suitable particle size distribution acceptance criteria for the drug substance cetirizine hydrochloride. (comment 4)

3. [redacted] is still deficient. A deficiency letter dated November 7, 2000, has been issued to the DMF holder.

4. Tighten the acceptance criterion for unspecified impurities in the pseudoephedrine hydrochloride drug substance to [redacted] and tighten the acceptance criterion for total unspecified impurities in the pseudoephedrine hydrochloride drug substance to <0.2%, to reflect the data observed. (comment 7)

5. Institute proper system suitability criteria to avoid large changes in number of theoretical plates and the tailing factor, and to increase assurance of the test results. We note that in the system suitability and intermediate precision for the test method for purity evaluation of pseudoephedrine hydrochloride drug substance (P187.12), the tailing factor and the number of theoretical plates decreased drastically between two analysts using a new and an aged column.

6. Describe the chromatographic conditions utilized and provide the peak resolution obtained for the pair ephedrine and pseudoephedrine with the test method for purity evaluation of pseudoephedrine hydrochloride drug substance (P187.12). This point pertains to analyses that yielded retention times for ephedrine shown on page 25 of your amendment dated October 11, 2000, for the Pfizer Method Transfer

, equal to phase through the column). (comment 18)

7. Provide a commitment to develop a better HPLC method to address the concerns with method P187.12 and to provide an adequate separation of the peaks corresponding to ephedrine and pseudoephedrine, with a resolution of at least in consideration of comments 5 and 6 above. The new validated method should be provided to the agency within 6 months of the date of this letter, along with methods validation data and comparative data generated from the two methods. (comment 15)

8. Tighten the acceptance criteria for impurities 1 and 2 observed in pseudoephedrine hydrochloride drug substance, by the TLC method (Test Method P 187.3,TLC), to <0.1% each as per ICH guideline Q3A. (comment 20)

9. Provide data for content from several representative batches of incoming pseudoephedrine hydrochloride drug substance, to justify the proposed acceptance criteria.

10. List only the validated column(s) (e.g., , in the description of the GC method (M60.19). If the column is claimed as equivalent to the provide data to support this claim.

The following comments pertain to the drug product:

11. Tighten the acceptance criteria for individual impurities in the drug product as follows, to conform to ICH guideline Q3B, and provide the acceptance criteria for the "total" categories listed below: (comments 27, 28)

Total specified degradants
Total unspecified (relative to cetirizine)
Total impurities
(includes unspecified degradants relative to cetirizine)

12. Provide dissolution data for cetirizine hydrochloride and pseudoephedrine hydrochloride obtained from testing at stages S2(L2) and S3(L3) levels for batches 8104, 8105 and 8107, where drug product dissolution at the S1 stage failed the proposed dissolution acceptance criteria. Provide data to demonstrate that the dissolution is not affected by the hardness of the tablet over the range of the acceptance criterion.

13. Tighten the cetirizine hydrochloride dissolution acceptance criterion to [redacted] at 30 minutes, as the criterion of [redacted] 60 minutes is not justified by your data. (comment 34)

14. Tighten the dissolution acceptance criteria for pseudoephedrine hydrochloride to the following:

    1 hour [redacted]
    2 hour [redacted]
    6 hour [redacted]

15. Set an appropriate acceptance criterion for moisture content of the drug product at release and stability, or provide data to demonstrate that moisture in the drug product does not adversely affect the hardness and dissolution of the drug product.

16. Identify clearly and chronologically all the changes made to the chromatographic method for the assay of degradants in the drug product during the stability studies, and provide comparative data from each version of the method.

17. Clarify the basis for different acceptance criteria [redacted] % with UCB method TDAAM0097 vs. [redacted] % with Pfizer method C157.2) for the degradants [redacted] in the drug product stability tables (pages 7-27 of the May 12, 2000, submission).

18. Update the specifications to include hardness with an appropriate acceptance criterion. Provide data to justify your claim that variations in hardness do not adversely affect the properties of the drug product. (comment 29)

19. Provide details on the number of tablets selected and the point of selection of tablets within a batch for various tests performed (e.g., beginning, middle and end). (comment 25)

20. Remove the phrase "or equivalent" in the description of the chromatographic column in the description of the test methods for the purity evaluation of pseudoephedrine hydrochloride (P187.21) and for quantification of impurities in the drug product (C 157.2). Only validated columns may be listed individually. (comment 13)

[redacted]

The following comments pertain to the Container/Closure System:

21. Provide appropriate results from USP <661> tests for polyethylene containers for the bottles to be used in the packaging of the drug product as per information provided by [redacted], amendment dated July 28, 2000).

22. Provide the complete chemical composition of the HDPE bottles for the drug product, including all additives, antioxidants, stabilizers and release agents etc., as per information provided by amendment dated July 28, 2000.

23. Identify and clearly distinguish the three different types of with the drug product

24. Provide stability data generated using drug product packaged in the other types of liddings, (comment 45)

25. are inadequate to support NDA 21-150. Deficiency letters, both dated January 9, 2001, have been sent to the DMF holders informing them of the deficiencies.

26. Clarify the dimensions of the used in closures for the HDPE bottles. The dimensional drawing provided in the amendment dated October 11, 2000, provided the thickness , however this is not consistent with the information present in the referenced DMF.

In addition, it will be necessary for you to submit revised draft labeling incorporating the revisions shown in the attached marked-up labeling and as described below:

27. Investigate the distribution and metabolism characteristics of pseudoephedrine to the extent possible, from the public domain. Include any information found to be adequate in the "Distribution" and "Metabolism" subsections of the PHARMACOKINETICS section of the package insert. Alternatively, if the information in the public domain is found to be inadequate, insert a statement in these subsections reflective of such a fact.

28. For all proposed labels and cartons, revise the printing so that the phrase "12 Hour" is the same font size and prominence as the trade name "Zyrtec-D™." The phrase "12 Hour" should appear on the same line, directly after the trade name. The print for the established name (cetirizine hydrochloride 5 mg and pseudoephedrine hydrochloride 120 mg Extended Release Tablets) should also be revised to appear commensurate in prominence with the trade name "Zyrtec-D™."

29. Redesign the label so that a box is not used to separate the phrase "Zyrtec-D™ 12 Hour" from the established name.

30. Increase the font size for the storage statement, dosage and use, and composition of the tablets to make them more legible and prominent. Decreasing the blank space on the container label may do this.

31. Improve the legibility of the lot and expiry date on the blister foil-front, as the information is not clear on the green background.

32. Clarify the purpose of the number that is present in the box situated above the lot and expiration date area on the 100 tablet commercial label.

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.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising and Communications, HFD-42
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

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, call Dr. Craig Ostroff, Project Manager, at 301-827-5580.

Sincerely,

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/

Robert Meyer
1/17/01 03:20:37 PM

APPEARS THIS WAY
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