

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-313

APPROVABLE LETTER



NDA 21-313

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Attention: Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

Dear Dr. Lamendola:

Please refer to your new drug application (NDA) dated December 8, 2000, received December 27, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clarinex-D 12 Hour (2.5 mg desloratadine and 120 mg pseudoephedrine sulfate) Extended-Release Tablets.

We acknowledge receipt of your submissions dated March 16, April 2, 6, and 27, May 22, and August 14 and 22, 2001.

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. The following comments pertain to the drug substances, desloratadine and pseudoephedrine sulfate.
 - a. Provide justification as to why the desloratadine median particle size acceptance criterion is _____ in this NDA at shelf life / _____ as compared to _____ for all other desloratadine NDAs), or modify this criterion to be consistent with the other applications.
 - b. Provide justification and supportive dosage form stability data for your selection of _____ for the desloratadine drug substance at release and shelf life.
 - c. Provide adequate data on different batches with their corresponding particle size distribution. Identify drug substance batches with different median particle size distributions and where each was used in different batches of drug product (i.e., clinical, biopharmaceutics, stability, etc.).
 - d. Provide a lower limit for the median particle size distribution and supportive pertinent data.
 - e. DMF _____ for pseudoephedrine sulfate is inadequate. A deficiency letter dated February 7, 2001, has been sent to the DMF holder.

- f. Provide comprehensive incoming acceptance specifications for pseudoephedrine sulfate.
2. The following comments pertain to the excipients used in the drug product.
- a. Provide clarification and documentation of the apparent discrepancy of the source of magnesium stearate. Section 4.B.2, page 2, states the magnesium stearate originates from _____, however, the letter from _____ section 4.F.1, page 101) states that the _____ brands are obtained from _____ originating from U.S. sources.
- b. Provide adequate acceptance specifications for critical excipients to ensure batch-to-batch consistency and performance of the drug product.
3. The following comments pertain to the manufacturing process of the drug product.
- a. Provide the range of times used for _____ This time should be defined for both the _____ process as well as _____
- b. Provide your rationale along with comparative data for utilizing _____ processes for manufacturing the _____
- c. Demonstrate that the _____ sublots (lots 2-9), manufactured subsequent to the first lot, are of equal quality as compared to the first subplot and also as compared to the single _____ lot.
- d. Clarify the fate of the excess _____ that may be left over during the manufacture of a commercial lot of the drug product.
- e. Provide limits on _____

_____ These times should be supported with stability data and incorporated into your SOP. The expiration dating period of the drug product manufactured with _____ Be aware that the expiration dating period of the drug product starts _____
- f. Perform _____ uniformity studies on the _____ at the minimum and maximum storage periods anticipated for the _____.
- g. Clarify the discrepancy for the in-process control on SR tablet weight. The executed batch records state the weight to be _____, whereas the table in volume 1.2, section 4.B.5, page 3, states the weight as _____. Provide updated batch records to reflect the latter. Clarify how the weight of the SR tablet layer is sampled during the _____ process.
- h. Perform process validation for the proposed _____ both IR

and SR) to assess the possibility of microbial contamination.

- i. Modify the SOP to state that the _____

- j. Define the range of time needed for _____ in the SOP, based on the amount of material processed in the _____
- k. Submit the revised master batch record that includes the above modifications. Highlight the revisions.

4. The following comments pertain to specifications of the drug product.

- a. Establish an acceptance criterion for total unspecified impurities in the drug product.
- b. The acceptance limits for _____ should be expressed in numerical values for release as well as shelf life.
- c. Provide suitable microbial test methods and limits for the drug product (e.g., USP <61>). No specifications for microbial limits and testing on the finished dosage form are provided in the current NDA.
- d. In order to make the specifications more readable with respect to degradants, add descriptors for the following degradants: _____

Resubmit updated specifications with the above changes.

5. The following comments pertain to the drug product method for appearance.

- a. Provide results for the _____ values of the reference standards.
- b. Provide details (including validation) for determining the quantitative description of color for the tablets.
- c. Due to the stability issues associated with desloratadine and color change of the pseudoephedrine sulfate layer, incorporate an appropriate quantitative method for establishing the appearance.

6. The following comments pertain to the dissolution method and detection by HPLC and UV analysis.

- a. Provide additional validation data for the alternate quantitation method that utilizes the _____ column maintained at _____. You are reminded that only validated columns should be listed in the methods.
- b. Provide for the robustness of the HPLC quantitation method by changing suitable parameters (_____)

- c. List the impurity, _____ in the specifications with appropriate limits.
 - d. Incorporate an acceptance criterion for total unspecified (e.g. _____).
10. The following comments pertain to the Determination of Residual _____¹ in Desloratadine Tablets by _____ (Method # _____)
 - a. Provide a listing of all equivalent columns proposed for the GC analysis of: _____
 - b. Provide an updated method number. Drug product specifications submitted in the update of April 27, 2001, list the method number to be # _____ However, no updates have been submitted to Method # _____
 - c. Modify the resolution values set for the peak pairs (_____, _____) in the system suitability criteria to reflect the observed values.
11. The following comments pertain to the packaging components.
 - a. Provide the acceptance specification for _____ closure liners. Acceptance specifications provided in vol. 1.3, section 4.B.7, page 9, indicate the inner seal liner as _____ only. Clarify this discrepancy.
 - b. Explain the unusually high increase in moisture _____ in bottle # 3, with a corresponding moisture permeation rate of _____ mg/day/liter, as reported in the container closure results for USP <661> testing.
 - c. Provide the chemical composition of the HDPE bottle (resin, colorant, mold number for the bottle, ratio of resin to colorant, additives, catalysts, release agents, etc.) to be used for the drug product. Alternatively, this information may be provided in a document termed "Confidential Materials Disclosure-Identifying the Mold number and Sequence Number," provided by the manufacturer of the bottle.
 - d. Provide the source, chemical composition, and appropriate specific CFR citations for the colorant used for the fabrication of the bottle. Alternatively, this information may be provided in an appropriate authorized drug master file (DMF).
12. The following comments pertain to the stability of the drug product.
 - a. Due to noted stability issues (e.g., _____) the proposed _____ packaging configuration is inappropriate and should be reconsidered.
 - b. Due to the noted stability issues, increase the number of batches for each of the proposed container-closure types in annual stability program to reflect the commercial production rate.
 - c. Revise the following statement mentioned in the section 4.B.8, page 2, of the OnGoing Stability Protocol: "If a product is packaged in multiple package sizes and types,

representative samples of each package size and type will be placed in the marketed package stability program in alternate years, so that all marketed packages are represented in the program." List each packaging configuration clearly in the stability protocol. (Refer to comment 12.b. above.)

- d. Provide a commitment to include the results of the post-approval stability protocol in the annual report.
- e. 
- f. Revise the acceptance criterion for moisture content. Alternatively, generate data to justify the proposed moisture criterion.
- g. Provide explanation(s) for the following observations: it is noted that impurities _____ are not observed when stored at _____ (in HDPE bottles or _____) but are observed when stored at _____. Similarly, impurity _____ is not detected when stored at _____, but is detected when stored at _____.
- h. Explain and justify the following trends observed during stability monitoring of the drug product. Further comments on the acceptance criteria and expiration dating period are being withheld pending receipt of adequate explanations and updated stability data (e.g., 9 month and 12 months) for production demonstration batches.
- (1) Moisture uptake increases with time for all batches when stored in _____
 - (2) Hardness increases significantly with time when tablets are stored under accelerated storage conditions (e.g., initial hardness for tablets for batch 76466-043 is _____ and at 6 months is _____).
 - (3) Dissolution rate decreases with time (e.g., release rate for pseudoephedrine component at the 2-hour and 6-hour time points decrease by approximately _____% and are close to the lower limit of the proposed acceptance limit).
- i. Provide an explanation for the following results: it appears that there is a difference in the pilot batches and the production demonstration batches in terms of moisture, hardness, dissolution (pseudoephedrine component at the 2- and 6-hour time points), and friability. For example, moisture levels increase for tablets stored in both HDPE bottles and _____ in production demonstration batches. In pilot batches, when stored in HDPE bottles, there is not a significant increase in moisture. Similarly, it appears that the probability of tablets failing friability during stability in _____ higher for production demonstration batches as compared to pilot batches.

- j. Provide an updated stability protocol that includes all pertinent modifications requested in this letter. The routine stability protocol should include testing at intermediate storage conditions (30°C/60%RH).
13. The following comments pertain to the desloratadine assay during manufacturing and stability.
- Provide the Batch Descriptor Sheets (containing information on the ingredients used for the preparation of _____ for drug product lot number 75882-051 (immediate release batch number 75882-044).
 - According to the tablet assay values and batch records, _____ of approximately _____ are noted for desloratadine. Implement appropriate changes to rectify this _____.
 - From the batch records for the preparation of immediate release _____ (batches 75882-45 and 75882-46), theoretical yield losses of _____ are noted. (The theoretical batch size is _____ and actual recovered weight is _____ and _____ kg, respectively.) Explain these losses and incorporate appropriate corrective measures to minimize them.
 - Provide the concentration of the active drug in the _____ that _____ Provide results from a _____ for the _____ obtained prior to _____.
 - For desloratadine during stability, the sum of the assay values and total degradants do not account for the total theoretical assay value (based on the batch records obtained at release). Provide data to account for loss of mass balance (e.g., unaccountable _____% in _____ of desloratadine in the drug product during stability).
14. The following comments pertain to the pseudoephedrine assay during manufacturing and stability.
- Provide the Batch Descriptor Sheet (containing information on the ingredients used for the preparation of _____) for drug product lot number 75882-051 (sustained release batch number 75882-047).
 - Based on the assay values and batch records, _____ of approximately _____ are noted for pseudoephedrine sulfate. Implement appropriate changes to rectify this _____.
 - From the batch records for the preparation of sustained release _____ (batches 75882-48 and 75882-49), theoretical yield losses of _____% are noted. (Theoretical batch size is _____ and actual recovered weight is _____ at _____ respectively.) Explain these losses and incorporate appropriate corrective measures to minimize them.
 - Provide the concentration of the active drug in the _____ that _____ Provide results from a _____ for the _____ obtained prior to _____.
 - Tighten the range for pseudoephedrine sulfate assay on stability to _____ to reflect the observed data.

15. Comments on the acceptance criteria for dissolution and hardness of the tablets are being withheld, pending availability of updated stability data (9, 12, and 18 months) for production demonstration batches 76466-042 and 76466-043. Once the data are available, the results will be fully evaluated for hardness, dissolution, and moisture content, and compared to the proposed acceptance criteria. Based on the findings, suitable acceptance limits will be determined.
16.
17. Provide a sample chromatogram of a mixture of degradants and representative chromatograms from stability studies, showing quantifiable separation of peaks as indicated in the reported stability results (e.g., RRT 0.69 and RRT 0.70). ✓
18. Provide stability data for the drug product stored in manufactured from and in bottles containing with .
19. Due to the instability of desloratadine in the presence of light, include a statement on the labeling to indicate that drug product should be protected from light.
20. Limit the levels of in the drug product, as we have identified these compounds as structural alerts. Alternatively, provide adequate qualification of the genotoxic potential (at least 2 *in vitro* genotoxicity assays with each individual drug product impurity up to the limit doses for each assay).
21. Submit the components (including batch numbers) of the Drixoral and solution formulations used in studies P00230 and P00446.
22. Submit a more complete analysis of the data to support a claim in the label for a lack of gender effect on the pharmacokinetics (PK) of pseudoephedrine (PSE). You are encouraged to pool all of the PSE pharmacokinetic data before making a statement of lack of gender effect on the PK on PSE. The analysis should be conducted taking into account the weight of the subjects.
23. Provide more references and/or literature information to support the statement in the label regarding the metabolism and elimination of PSE. Also, include supporting evidence for the need for dose adjustment in renally impaired patients.
24. From the overall desloratadine pharmacokinetic database, it appears that a substantial subset of patients had significantly higher drug exposure (AUC) than most patients to desloratadine and very low levels of 3-hydroxydesloratadine. The exposure to desloratadine resulting from multiple doses in adults who are poor metabolizers is estimated to be six- to nine-fold the

median AUC in adults with apparent normal metabolism. Moreover, there are no data to identify the underlying cause of poor metabolism, and so there is no means of prospectively identifying those patients who may have such high levels of exposure to desloratadine. If these patients are inherently poor metabolizers of desloratadine, then the number of patients who experience these high exposure levels may be much greater, particularly if there is a deficient metabolic pathway involved that may be vulnerable to inhibition with concomitant medications.

You are encouraged to determine the mechanism accounting for higher levels of drug exposure observed in some patients, and to assess the potential for drug-drug interactions that might be expected based on the explanatory mechanism. You should also provide data from desloratadine and loratadine to justify the safety of these high levels of desloratadine exposure.

25. The information requested in comment 24 also will be pertinent to other NDAs for desloratadine products with adult indications (currently, NDAs 21-165, 21-297, 21-312, and 21-363).
26. 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 investigator. Satisfactory inspections will be required before this application may be approved.
27. The following preliminary comments pertain to labeling of the drug product. Additional comments may be forthcoming after you have responded to the above deficiencies.
 - a. In the HOW SUPPLIED section of the labeling and on the package labels, reference should be made to "see USP Controlled Room Temperature."
 - b. Before complete comments on labeling of the drug product can be given, please submit color representations of label and labeling mock-ups.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). You are advised to contact the Division regarding the extent and format of your safety update prior to responding to this letter.

You are reminded of your commitment under NDA 21-165 to submit the final study report for the ongoing mouse carcinogenicity study within 3 years of approval of NDA 21-165 or within 3 years of study initiation, whichever occurs first.

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, call Mr. David Hilfiker, Regulatory Project Manager, at (301) 827-1084.

Sincerely yours,

{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

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/s/

Robert Meyer
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