

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-375**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

Wyeth Consumer Healthcare  
Five Giralda Farms  
Madison, NJ 07940

Attention: David Smith, Ph.D.  
Director, Regulatory Affairs

Dear Dr. Smith:

Please refer to your new drug application (NDA) dated August 23, 2001, received September 4, 2001, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Alavert (loratadine) Orally Disintegrating Tablets.

We acknowledge receipt of your submissions dated October 3, 2001, January 11, 17, 22 and 31, February 4, 7 and 21 (2), March 8 and 11, May 3, 13, 23, 24, and 31, June 7, 10, and 28, July 2, 5(2), 9, 11, 18, and 19 (2), August 15, September 5, 19, and 20, October 14 (2), 28, and 31 (2), and November 6 and 22, 2002.

The December 13, 2002, submission constituted a complete response to our December 12, 2002, action letter.

This NDA provides for the over-the-counter use of Alavert (loratadine) Orally Disintegrating Tablets for the temporary relief of symptoms of hay fever or other upper respiratory allergies: runny nose, sneezing, itchy, watery eyes, and itching of the nose or throat.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text. We remind you to incorporate the following revision into the label at the next printing or within 6 months, whichever is sooner.

Remove the word "Antihistamine" from the parenthesis on the carton Label.

The final printed labeling (FPL) must be identical to, except for including the revisions indicated, the enclosed labeling (immediate container and carton labels) submitted on October 14, 2002.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. 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. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "FPL for approved NDA 21-375." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your post-approval follow-up agreement in your submission dated November 13, 2002, to submit information in each quarterly periodic safety report for the first three years after approval on reports from various sources of the occurrence of hypospadias cases.

In addition, we request that you submit two copies of the introductory promotional materials you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Pulmonary and Allergy Drug Products and one to the Division of Over-the-Counter Drug Products.

Oversight of this application is being transferred to the Division of Over-the-Counter Drug Products.

If you have any questions, call Elaine Abraham, Regulatory Management Officer, at (301) 827-2301.

Sincerely,

Sincerely,

*{See appended electronic signature page}*

*{See appended electronic signature page}*

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

Badrul A. Chowdhury, M.D., Ph.D.  
Acting Director  
Division of Pulmonary and Allergy  
Drug Products  
Center for Drug Evaluation and Research

Enclosure - Labeling

**CENTER FOR DRUG EVALUATION AND  
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-375

Wyeth Consumer Healthcare  
Five Giralda Farms  
Madison, NJ 07940

Attention: David Smith  
Director, Regulatory Affairs

Dear Mr. Smith:

Please refer to your new drug application (NDA) dated August 23, 2001, received September 4, 2001, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Alavert (loratadine) Orally Disintegrating Tablets.

We acknowledge receipt of your submissions dated February 4 and 21, March 8, and May 3, 13, 24 and 31, 2002.

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:

1. The following comments pertain to the drug substance:
  - a. Describe the color quantitatively [e.g., American Public Health Association (APHA) color index]. \_\_\_\_\_
  - b. Tighten the chromatographic impurities as follows:  
  
\_\_\_\_\_  
\_\_\_\_\_
  
2. The following comments pertain to the release specifications for the drug product.
  - a. Establish appropriate specifications for ' \_\_\_\_\_ ' as a release parameter.
  - b. " \_\_\_\_\_ " Describe the color quantitatively such as by APHA color index.
  - c. Tighten the ' \_\_\_\_\_ ' to NMT \_\_\_\_\_ Monitor the parameter at release and at expiry.
  - d. Tighten the ' \_\_\_\_\_ ' Monitor the parameter at release and at expiry.
  - e. Tighten the acceptance criterion for each impurity to < 0.1% to reflect actual data.
  - f. Tighten the acceptance criterion for each individual unknown impurity to < 0.1% to reflect actual data.
  - g. Tighten the acceptance criterion for total impurities to NMT \_\_\_\_\_
  - h. Provide an updated specifications sheet that reflects the above changes



- (2) Replace the phrase \_\_\_\_\_ with the phrase "Orally Disintegrating." This is the established name currently recognized for this dosage form.
- c. Regarding the left flap:
- (1) Add an asterisk notation ("\*") after the phrase "Non-drowsy" to direct the consumer to the statement on the PDP.
- (2) Replace the phrase \_\_\_\_\_ with the phrase "Orally Disintegrating." This is the established name currently recognized for this dosage form.
- d. Regarding the right flap, add an asterisk notation ("\*") after the phrase "Non-drowsy" to direct the consumer to the statement on the PDP.
- e. Regarding the upper half of the back panel:
- (1) Revise the first sentence to read as follows: "Alavert Allergy provides 24 hours of allergy symptom relief without causing drowsiness when taken as directed."
- (2) After the first sentence on this panel, add the following: "(See Drug Facts below.)" This statement is necessary to direct the consumer to more information concerning the non-drowsiness claim.
- (3) Revise the second sentence to read: "It contains prescription-strength loratadine."
- (4) \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_
- f. Regarding the "Drug Facts" panel:
- (1) Revise the statement under *Active ingredient (in each tablet)* so that only a single space and no commas appear between "Loratadine" and "10 mg."
- (2) Under *Purpose*, delete the phrase \_\_\_\_\_ as it is not part of the pharmacological category.
- (3) Under *Uses*, remove the bullet before the word "temporarily."
- (4) Under *Warnings*, add the subheading **Do not use** followed by the statement "if you have ever had an allergic reaction to this product or any of its ingredients." Remove reference to \_\_\_\_\_ under the subheading **Ask a doctor before use if you have.**
- (5) Under *Warnings*, immediately after the bulleted statement appearing under the subheading **Ask a doctor before use if you have**, add the following statement: "Your doctor should determine if you need a different dose."
- (6) Under *Warnings*, **When using this product**, remove the bold type for the bulleted statement "do not use more than directed."
- (7) Under *Warnings*, insert the subheading **Stop use and ask a doctor if** followed by the text "an allergic reaction to this product occurs. Seek medical help right away."

(8) Under *Directions*:

- (i) Rearrange the statements for clarity.
- (ii) Delete the bulleted statement "tablet \_\_\_\_\_ in mouth."
- (iii) Add a third population group and text in the dosing table to read: "consumers who have liver or kidney disease: ask a doctor."

g. Include a provision for a lot number and expiration date.

7. Replace the phrase \_\_\_\_\_ with the phrase "Orally Disintegrating Tablet" on the proposed blister card label for the Alavert™ Allergy product.

8. \_\_\_\_\_"

9. Where appropriate on the carton and blister card labels, replace the previous name of the company, "Whitehall-Robins Healthcare," with the new company name "Wyeth Consumer Healthcare."

As conveyed to you previously, we consider the use of the name "Dimetapp" as a tradename for OTC loratadine to be inappropriate and to have potential safety issues. The Dimetapp brand name is already well established as a marketed product generally containing brompheniramine.

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 the Division of Pulmonary and Allergy Drug Products regarding the extent and format of your safety update prior to responding to this letter.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with the Division of Pulmonary and Allergy Drug Products 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.

We are waiving the pediatric study requirement for this action for this application for patients ages two years to 12 years because an appropriate dosage form and pediatric information already exists. We are waiving the pediatric study requirement for this action for this application for patients less than two years of age because pediatric information already exists.

If you have any questions, contact Anthony M. Zeccola, Regulatory Management Officer, at 301-827-1058.

Sincerely,

~~See appended electronic signature page~~ ~~See appended electronic signature page~~

Jonca Bull, M.D.  
Director  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

Robert Meyer, M.D.  
Director  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Jonca Bull  
7/3/02 03:20:34 PM

Robert Meyer  
7/3/02 03:28:57 PM

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**21-375**

**APPROVABLE LETTER 2**



NDA 21-375

Wyeth Consumer Healthcare  
Five Giralda Farms  
Madison, NJ 07940

Attention: David Smith  
Director, Regulatory Affairs

Dear Mr. Smith:

Please refer to your new drug application (NDA) dated August 23, 2001, received September 4, 2001, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Alavert (loratadine) Orally Disintegrating Tablets.

We acknowledge receipt of your submissions dated July 5, 11, and 19, and September 5, 2002. Your submission of July 19, 2002, constituted a complete response to our July 3, 2002, action letter.

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. The comments in parentheses refer to your responses in your amendment dated July 19, 2002:

1. \_\_\_\_\_ is very subjective. Describe the color in a quantitative manner, e.g., APHA color index. [Responses 1(a) & 2(b)]
2. The following comments pertain to Response 1(b). Tighten the impurity specifications as follows:

\_\_\_\_\_  
\_\_\_\_\_

3. Provide drug product batch release and stability data for \_\_\_\_\_ and \_\_\_\_\_. Provide data to demonstrate that when the product is in the blister package, the environment does not promote microbial growth. As requested previously, tighten the \_\_\_\_\_ and \_\_\_\_\_ to not more than (NMT) \_\_\_\_\_ and NMT \_\_\_\_\_ respectively. [Responses 2(c) and 2(d)]
4. As previously requested, tighten the acceptance criterion for total impurities in drug product to

NMT \_\_\_\_\_ Stability data indicate that the total impurities level does not exceed \_\_\_\_\_ at 24 months. [Responses 2(g) & 3(d)]

5. Provide updated specification sheets that reflect all of the above modifications. [Response 2(h)]

6. The following comments pertain to the stability protocol [Response 3(c)]:

a. Modify acceptance criteria for \_\_\_\_\_ and \_\_\_\_\_ as indicated above.

b. Provide an updated post-approval stability protocol which reflects all of the above comments.

7. Provide an updated method validation package once the above issues are resolved. [Response 4]

8. The 12-, 24-, and 48-count draft carton labels for Alavert Allergy product are not acceptable. Submit revised labeling for these packages as follows:

a. Trade name and red ribbon phrase: \_\_\_\_\_ The trademark phrase " \_\_\_\_\_ must not appear in the ribbon sections of the Alavert Allergy 12-, 24- and 48-count draft carton labels. Instead, you may include this phrase as part of the proprietary name of this product (i.e., "Alavert Allergy \_\_\_\_\_ ") to specifically designate an orally disintegrating tablet dosage formulation.

The Agency believes that the trademark phrase \_\_\_\_\_ is intended to specifically correspond to the proprietary name "Alavert Allergy" and to the orally disintegrating tablet dosage formulation. As such, the phrase \_\_\_\_\_ is considered an extension to the proprietary name "Alavert Allergy".

Accordingly, the Agency has no objection to the trademark phrase \_\_\_\_\_ when used as part of the proprietary name (i.e., "Alavert Allergy \_\_\_\_\_ ") to specifically designate an orally disintegrating tablet dosage formulation. This revised trade name must appear wherever the trade name appears on the **carton and blister card** labels.

b. On the bottom panel of the carton labels:

(1) The phrase "...when taken as directed" must appear in bold type to highlight the manner of use that will generally result in non-drowsiness.

(2) Revise the sentence "The mint flavored \_\_\_\_\_ melts in your mouth" to read: "The mint flavored Alavert Allergy; \_\_\_\_\_ melts in your mouth". See discussion in 8(a) above.

c. Drug Fact Labeling:

Under **Other Information**, add, "Keep in a dry place" as a separate bulleted statement for an additional storage condition. This storage condition was recommended for the prescription product.

d. Under the heading Directions:

- (1) In the first bulleted statement, the first letter in the word "Tablet" should appear in lowercase.
- (2) In the dosing table:
  - (a) In the first population group, the first letter in the word "Adult" should appear in lowercase.
  - (b) In the second population group, the first letter in the words "Children" and "Ask" should appear in lowercase.
  - (c) In the third population group, the letter in the words "Consumers" and "Ask" should appear in lowercase.

e. Under the heading "Questions or comments", the first letter in the word "Call" should appear in lowercase.

9. We note that although the popular "Dimetapp" name is now associated with products that offer relief for a wide range of symptoms, consumers may not be able to distinguish a "Dimetapp" product that contains a first-generation antihistamine product that causes drowsiness (e.g., brompheniramine) from a second-generation "Dimetapp" product that contains a non-drowsy antihistamine ingredient (e.g., loratadine). The Agency believes that it is essential that consumers be fully aware of the distinction between a product that causes drowsiness and a product that does not, particularly with regard to activities that require full attention (e.g., driving or operating machinery). To avoid possible consumer confusion we believe that it is in the best interest of consumers to not have the same brand name "Dimetapp" for both a sedating and a non-sedating antihistamine drug product, even if modified with descriptive qualifiers. As conveyed to you previously, we consider the use of the name "Dimetapp" as a tradename for OTC loratadine to be inappropriate and to have potential safety issues. The Dimetapp brand name is already well established as a marketed product generally containing brompheniramine.

The brand name "Children's Dimetapp Allergy" is not acceptable. A "children's" brand name could lead to a proliferation of other products with names based on specific age groups within the intended population range. We believe that marketing the product as a children's product is misleading and may lead to consumer confusion, since there is no difference in the formulation or dosing regimen of the adult product (Alavert Allergy) and the children's product (Children's Dimetapp Allergy).

10. Clarify for which study/ies financial disclosure information was submitted. Financial disclosure information is required for the study that establishes bioequivalence with the reference listed drug.

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 of Pulmonary and Allergy Drug Products regarding the extent and format of your safety update prior to responding to this letter.

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

NDA 21-375

Page 4

We are waiving the pediatric study requirement for this action for this application for patients ages two years to 12 years because an appropriate dosage form and pediatric information already exists. We are waiving the pediatric study requirement for this action for this application for patients less than two years of age because pediatric information already exists.

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 Anthony M. Zeccola, Regulatory Management Officer, at 301-827-1058.

Sincerely,

~~(See appended electronic signature page)~~

~~(See appended electronic signature page)~~

Jonca Bull, M.D.  
Director  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

Robert Meyer, M.D.  
Director  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Jonca Bull  
9/18/02 11:59:36 AM

Robert Meyer  
9/18/02 09:51:27 PM

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RESEARCH**

*APPLICATION NUMBER:*

**21-375**

**TENTATIVE APPROVABLE LETTER**



NDA 21-375

Whitehall-Robbins  
Five Giralda Farms  
Madison, NJ 07940

Attention: David Smith, Ph.D.  
Director, Regulatory Affairs

Dear Dr. Smith:

Please refer to your new drug application (NDA) dated August 23, 2001, received September 4, 2001, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Alavert (loratadine) Orally Disintegrating Tablets.

We acknowledge receipt of your submissions dated January 11, 17, and 22, February 4, 7, and 21(2), March 8, May 3, 13, 23, 24, and 31, June 28, July 11 and 19, September 5, October 14 and 31, and November 6 and 22, 2002. Your submission of October 14, 2002, constituted a complete response to our September 18, 2002, action letter.

This NDA provides for the over-the-counter use of Alavert (loratadine) Orally Disintegrating Tablets for the temporary relief of symptoms of hay fever or other upper respiratory allergies: runny nose, sneezing, itchy, watery eyes, and itching of the nose or throat.

We completed our review of this application, as amended. It is tentatively approved under 21 CFR 314.105 for use as recommended in the agreed upon labeling submitted October 14, 2002. This determination is contingent upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices of the facilities used in manufacturing and testing of the drug product) and is, therefore, subject to change on the basis of any new information that may come to our attention.

The listed reference drug product upon which you based your application is subject to a period of patent protection and therefore final approval of your application under section 505(c)(3) of the Act (21 U.S.C. 355(c)(3)) may not be made effective until the period has expired, i.e., December 19, 2002.

Prior to December 19, 2002, or when requested, submit an amendment to this application identifying changes, if any, in the conditions under which your product was tentatively approved. This information should include updated labeling, chemistry, manufacturing and controls data, and a safety update.

Consider amending your NDA prior to December 19, 2002, with updated labeling that reflects the advice provided in comment 2.b. of our October 28, 2002, facsimile correspondence. Otherwise, after

you receive final approval implement this change in your labeling in the next printing or within 6 months, whichever is sooner.

We remind you of your post-approval follow-up agreement in your submission dated November 13, 2002, to submit information in each quarterly periodic safety report for the first three years after approval on reports from various sources of the occurrence of hypospadias.

Any significant change in the conditions outlined in this NDA requires our review before final approval may be granted.

Before we issue a final approval letter, this NDA is not deemed approved. If you believe that there are grounds for issuing the final approval letters before December 19, 2002, you should amend your application accordingly.

This product may be considered misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before final approval.

If you have any questions, call Anthony M. Zeccola, Regulatory Management Officer, at (301) 827-2301.

Sincerely,

*{See appended electronic signature page}*

*{See appended electronic signature page}*

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

Badrul Chowdhury, M.D., Ph.D.  
Acting Director  
Division of Pulmonary and Allergy  
Drug Products  
Center for Drug Evaluation and Research

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/s/

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Charles Ganley  
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Badrul Chowdhury  
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