CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-300

LABELING REVIEW(S)

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-300 Date of Submission: December 17, 2001

Applicant's Name: Altana Inc.

Established Name: Fluticasone Propionate Ointment, 0.005%

Labeling Deficiencies:

1. CONTAINER (15 g, 30 g, 60 g)

   Revise the name to read "Fluticasone Propionate Ointment, 0.005%".

2. CARTON (15 g, 30 g, 60 g)

   See the comment under container.

3. INSERT

   a. GENERAL

      i. Please note that the following comments are based on the last approved insert labeling for Cutivate® Ointment. (approved December 9, 2001) Refer to the website listed at the end of this letter.

      ii. Replace "Fluticasone Propionate Ointment" with "fluticasone propionate ointment" throughout the text. Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when USAN name stands alone as on labels or in the title of the package insert.

   b. CLINICAL PHARMACOLOGY

      i. Please add the following paragraph as the new second paragraph;

      Fluticasone propionate is lipophilic and has a strong affinity for the glucocorticoid receptor. It has weak affinity for the progesterone receptor, and virtually no affinity for the mineralocortocoid, estrogen, or androgen receptors. The therapeutic potency of glucocorticoids is related to the half-life of the glucocorticoid-receptor complex. The half-life of the fluticasone propionate-glucocorticoid receptor complex is approximately 10 hours.

      ii. Please refer to the Cutivate® Ointment insert labeling approved December 9, 2001, for the pharmacokinetics subsection and add the following sections; Absorption, Distribution, Metabolism and Excretion.

   c. PRECAUTIONS

      i. Third paragraph

      Please change this paragraph to be the same as the innovator's.

      ii. Fourth paragraph

      Please relocate the fourth paragraph "If HPA axis suppression..." to appear immediately after the second paragraph.

iii. Fourth paragraph, sixth sentence

Please make editorial changes (move sentence to one line).

iv. Fifth paragraph

Replace ——— with "pediatric patients".....

v. Sixth paragraph

Please add the following paragraph as the new sixth paragraph, "Fluticasone propionate ointment, 0.005% may cause local cutaneous adverse reactions (see ADVERSE REACTIONS)."

vi. Last paragraph, first sentence:

Replace "———— with "presence".

vii. Information for patients

Please add the following statements;

5. This medication should not be used on the face, underarms, or groin areas unless directed by a physician.

6. As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, contact the physician.

viii. Geriatric Use

Please include this subsection to appear immediately after the Pediatric Use subsection:

A limited number of patients above 65 years of age (n = 203) have been treated with fluticasone propionate ointment in US and non-US clinical trials. While the number of patients is too small to permit separate analysis of efficacy and safety, the adverse reactions reported in this population were similar to those reported by younger patients. Based on available data, no adjustment of dosage of fluticasone in geriatric patients is warranted.

d. DOSAGE AND ADMINISTRATION

Please include the subsection, Geriatric Use, with the following statement:

" In studies where geriatric patients (65 years of age or older, see PRECAUTIONS) have been treated with fluticasone propionate ointment, safety did not differ from that in younger patients; therefore, no dosage adjustment is recommended.

Please revise your labeling, as instructed above, and submit labels and labeling in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		x	
Is this name different than that used in the Orange Book?			x
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	

Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			x
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section? [not scored]			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?			x
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	

Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		x	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		x	

FOR THE RECORD:

1. MODEL LABELING – Cutivate Ointment® (NDA 19-957/S-009) approved on December 9, 2001.

2. This drug product is **not** the subject of a USP monograph.

3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing in Vol. A.1.4; Section 7, page 1180.

4. PATENTS/EXCLUSIVITIES:

Patent Data – NDA 19-957

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4335121	November 14, 2003	None	None	Paragraph III	Same as

Exclusivity Data– NDA 19-957

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	*N/A*	*None*

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   Both RLD and the ANDA: Store at controlled room temperature 2° to 30°C (36° and 86°F).

6. PACKAGING CONFIGURATIONS

   The RLD packages its product in 15 g, 30 g, and 60 g tubes.
   The applicant is proposing to market its product in 15 g,
   30 g, and 60 g sealed, aluminum tubes. (Vol A. 1.4; Section 13; Page 1540)

7. FINISHED DOSAGE MANUFACTURING FACILITY

   Altana, Inc. is the sole manufacturer for this product (Vol A.1.4; Section 9, page 1327).

Date of Review: 6/19/02

Date of Submission: 12/17/01

Primary Reviewer: Michelle Dillahunt

Michelle Dillahunt

Date: June 27, 2002

Team Leader: John Grace

John J Grace

Date: 7/1/2002

cc:

ANDA: 76-300
DUP/DIVISION FILE
HFD-613/MDillahunt/JGrace (no cc)
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Review

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-300

Date of Submission: July 29, 2002 - Amendment

Applicant's Name: Altana Inc.

Established Name: Fluticasone Propionate Ointment, 0.005%

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

- Do you have 12 Final Printed Labels and Labeling? Yes
- Container Labels: 15 g, 30 g, and 60 g satisfactory as of July 29, 2002 submission
- Carton Labeling: 15 g, 30 g, and 60 g satisfactory as of July 29, 2002 submission
- Professional Package Insert Labeling: Satisfactory as of July 29, 2002 submission.

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Cutivate Ointment 0.005%
- NDA Number: 19-957 / S009
- NDA Drug Name: Fluticasone propionate ointment, 0.005%
- NDA Firm: Glaxo Wellcome Inc.
- Date of Approval of NDA Insert and supplement #009: December 9, 2001
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Basis of Approval for the Container Labels: Side-by-side comparison
- Basis of Approval for the Carton Labels: Side-by-side comparison
- Revisions needed post-approval: No
- Patents/Exclusivities: Refer to chart below.

Patent Data – NDA 19-957

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4335121	November 14, 2003	NONE	NONE	Paragraph III	Same as

Exclusivity-Data – NDA 19-957

Code	Reference	Expiration	Labeling Impact
NONE	NONE	NONE	NONE

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?			X
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
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Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
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Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
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Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X

Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
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Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
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A numbering error occurred in the "FOR THE RECORD" section.
No page is missing.

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Altana, Inc. is the sole manufacturer for this product (Vol A.1.4; Section 9, page 1327).

Date of Review: 9/6/02 **Date of Submission: July 29, 2002 (Amendment)**

Primary Reviewer: B. Weetman **Date:** 9/6/02

Team Leader: John D. Grace **Date:** 9/9/2002

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cc:

ANDA: 76-300
DUP/DIVISION FILE
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Review

APPEARS THIS WAY
ON ORIGINAL