

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-658

PROPRIETARY NAME REVIEW(S)

Division of Medication Errors and Technical Support (DMETS)
White Oak Bldg 22, Mail Stop Room 4447
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

PROPRIETARY NAME, LABEL AND LABELING REVIEW

DATE OF REVIEW: October 26, 2007
NDA#: 21-658
NAME OF DRUG: Alvesco (Ciclesonide Inhalation Aerosol), 80 mcg and 160 mcg
NDA HOLDER: Sanofi-Aventis Pharmaceuticals

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

I. INTRODUCTION:

This consult was written in response to a request from the Division of Pulmonary and Allergy Products (HFD-570), for a final assessment of the proprietary name, Alvesco, regarding potential name confusion with other proprietary or established drug names. Container labels and insert labeling were provided for review and comment. Alvesco was found acceptable by DMETS in OSE review 04-0022 dated March 29, 2004.

PRODUCT INFORMATION

Alvesco is an orally inhaled corticosteroid indicated for the maintenance treatment of asthma as prophylactic therapy in adults. The usual dose of Alvesco is 80 mcg twice daily to 320 mcg twice daily. Alvesco is supplied in 80 mcg or 160 mcg metered-dose inhalation aerosols.

b(4)

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of the internet, several standard published drug product reference texts^{1,2} as well as several FDA databases^{3,4} for existing drug names which sound-alike or look-alike to Alvesco to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁵. The Saegis⁶

¹ MICROMEDEX Integrated Index, 2007, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-07, and the electronic online version of the FDA Orange Book.

⁴ Phonetic and Orthographic Computer Analysis (POCA)

⁵ WWW location <http://www.uspto.gov/tmdb/index.html>.

Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name. Following completion of these initial components, an overall risk assessment is conducted that does not evaluate the name alone. The assessment considers the findings from above and more importantly integrates post-marketing experience in assessing the risk of name confusion, product label/labeling, and product packaging. Because it is the product that is inserted into the complex and unpredictable U.S. healthcare environment, all product characteristics of a drug must be considered in the overall safety evaluator risk assessment.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Alvesco. Potential concerns regarding drug marketing and promotion related to the proposed name(s) were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the name, Alvesco, acceptable from a promotional perspective.
2. Since the previous review, the Expert Panel identified fifteen proprietary names that were thought to have the potential for confusion with Alvesco. They are: Alvesin, _____, _____, Alvercol, Amevive, Almora, Almacone, Alferon N, Aloe Vera, Alfuzocin, Aliskiren, Zavesca, Alex, Lescol and Lescol XL.

B. SAFETY EVALUATOR RISK ASSESSEMMENT

In reviewing the proprietary name Alvesco, the following fifteen names were identified as having similar appearance and/or sound to Alvesco. They are: Alvesin, _____, _____, Alvercol, Amevive, Almora, Almacone, Alferon N, Aloe Vera, Alfuzocin, Aliskiren, Zavesca, Alex, Lescol and Lescol XL. b(4)

In the initial analysis of these names DMETS determined the following 15 names, Alvesin, _____, _____, Alvercol, Amevive, Almora, Almacone, Alferon N, Aloe Vera, Alfuzocin, Aliskiren, Zavesca, Alex, Lescol, and Lescol XL would not be considered further for the following reasons. b(4)

- Zavesca was previously reviewed in comparison to Alvesco in OSE review 04-0022.
- In addition to lacking orthographic and/or phonetic similarities with Alvesco: _____, Amevive, Almacone, Alferon N, Aloe Vera, Alfuzocin, Aliskiren, Alex, Lescol, and Lescol XL do not share product commonalities such as dosage form, route of administration, product strength, usual dose, dosing frequency, and/or indication of use.

⁶ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

• Alvesin and Alvercol are foreign products that do not share product commonalities such as dosage form or indication of use with Alvesco.

• ~~Alvesin~~ was a proposed name that was found unacceptable by DMETS in OSE review 05-11. The ANDA was approved using the established name.

Thus, DMETS finds the name Alvesco acceptable.

b(4)

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels and insert labeling of Alvesco, DMETS focused on human factors and safety issues relating to medication errors. DMETS has identified the following areas of improvement, which may minimize potential user error.

A. Container Label (80 mcg and 160 mcg)

1. Decrease the prominence of the graphic to the right of the proprietary and established names. As currently presented, it is more prominent than important information such as the established name, product strength, and net quantity.
2. The font utilized for the established name makes it difficult to read which may lead to misinterpretation. Revise the font to a font that easier to read and that it is not italicized.
3. Debold the font utilized for the net quantity (i.e. One 6.1 g Canister) and the total number of actuations (i.e. 60 Metered Actuations) in order to make the information easier to read.
4. Revise the product strength to read "80 mcg/actuation" or "160 mcg/actuation" so that practitioners and patients are aware of how much drug product is delivered per actuation.

B. Carton Labeling (80 mcg and 160 mcg)

1. See comments A-1 through A-4.
2. Revise the second sentence on the back display panel to read "The XX mcg strength of Alvesco delivers XXX mcg from the valve and XX mcg of ciclesonide from the actuator. As currently presented (Alvesco 80 mcg and Alvesco 160 mcg) it appears that the product strength is part of the proprietary name.

C. Package Insert Labeling - Dosage and Administration Section, Dosing Table

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2. Revise the term "Adults and Adolescents" to read "Adults and Adolescents 12 years and older" in order to clarify at what age adolescents should take the increased dose.

b(4)

D. Patient's Instructions for Use

1. Ensure that the Patient's Instructions for Use have been submitted to the Division of Surveillance, Research, and Communication Support for review and comment on the comprehensibility of the instructions.
2. The Patient's Instructions for Use contain very specific instructions that must be followed for correct use of this product. Misinterpretation of the instructions may lead to medication errors. The potential for medication errors may be minimized by including additional illustrations for each step in the "How To Use Alvesco" section in the Patient's Instructions for Use.

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

/s/

Linda Kim-Jung
12/14/2007 03:32:49 PM
DRUG SAFETY OFFICE REVIEWER

Signing for Kristina Arnwine in her absence 12/14/07.

Denise Toyer
12/14/2007 03:55:11 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
12/14/2007 04:42:34 PM
DRUG SAFETY OFFICE REVIEWER

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED: January 29, 2004	DESIRED COMPLETION DATE: March 29, 2004 PDUFA DATE: October 23, 2004	ODS CONSULT #: 04-0022
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TO: Badrul Chowdhury, MD
Director, Division of Pulmonary and Allergy Drug Products
HFD-570

THROUGH: Colette Jackson
Project Manager
HFD-570

PRODUCT NAME: Alvesco™ (Ciclesonide Inhalation Aerosol) _____, 80 mcg, and 160 mcg	NDA SPONSOR: Aventis Pharmaceuticals, Inc. b(4)
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NDA#: 21-658

SAFETY EVALUATOR: Kristina C. Arnwine, PharmD

RECOMMENDATIONS:

- DMETS has no objections to the use of the proprietary name, Alvesco™. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
- DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.
- DDMAC finds the proprietary name Alvesco™ acceptable from a promotional perspective.

Carol Holquist, RPh Deputy Director Division of Medication Errors and Technical Support Office of Drug Safety Phone: (301) 827-3242	Fax: (301) 443-9664	Jerry Phillips, RPh Associate Director Office of Drug Safety Center for Drug Evaluation and Research Food and Drug Administration
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Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: February 25, 2004

NDA# 21-658 **b(4)**

NAME OF DRUG: Alvesco™ (Ciclesonide Inhalation Aerosol), ~~_____~~ 3, 80 mcg, and 160 mcg

NDA HOLDER: Aventis Pharmaceuticals, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Pulmonary and Allergy Drug Products (HFD-570), for assessment of the proprietary name, Alvesco, regarding potential name confusion with other proprietary or established drug names. Container labels, carton and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Alvesco is a synthetic corticosteroid for inhalation indicated for the maintenance treatment of asthma as prophylactic therapy in adult _____ **b(4)**

relief of acute bronchospasm. Alvesco is supplied in metered dose inhalers in _____ 80 mcg, and 160 mcg strengths per inhalation containing either 60 or 120 inhalations per canister.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2}, as well as several FDA databases³ for existing drug names which sound-alike or look alike to Alvesco to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁴. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise

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² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.

was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Alvesco. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC had no promotional concerns regarding the proprietary name Alvesco.
2. The Expert Panel did not identify any proprietary names that were thought to have the potential for confusion with Alvesco.

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. The POCA identified Zavesca and Advicor which were considered to have significant phonetic or orthographic similarities to Alvesco. These products are listed in table 1 (see below), along with the dosage forms available and usual dosage.

b(4)

Table 1: Potential Sound-Alike/Look-Alike Names Identified by POCA

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Alvesco	Ciclesonide Inhalation Aerosol 80 mcg, and 160 mcg	2 puffs by mouth daily	
Zavesca	Miglustat Capsules 100 mg	1 capsule by mouth three times daily	SA
Advicor	Niacin/Lovastatin Tablets 500/20 mg, 750/20 mg, and 1000/20 mg	1 tablet by mouth at bedtime	LA

*Frequently used, not all-inclusive.
 **L/A (look-alike), S/A (sound-alike)

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Alvesco with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 125 health care professionals (pharmacists, physicians, and nurses). This exercise was

conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Alvesco (see page 4). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p>Outpatient RX:</p> <p>Alvesco 80mcg as dir daily #1</p>	<p>“...third prescription is Alvesco 80 mcg use as directed daily, #1...”</p>
<p>Inpatient RX:</p> <p>Alvesco 80mcg as needed daily</p>	

2. Results:

Twenty-two respondents interpreted the proposed name as Alveno. Alveno sounds and looks similar to the currently marketed product Aveeno. See appendix A for the complete listing of interpretations from the verbal and written studies.

E. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Alvesco, the Expert Panel did not identify any names as having the potential to sound or look similar to Alvesco. Nor were any additional names identified through independent review. However, a POCA search identified the names Zavesca and Advicor as having phonetic or orthographic similarities to Alvesco. Upon further review, the similarities of these names were not significant due to differences between the names, dosage form and usual doses and thus will not be discussed any further in this review.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any currently marketed U.S. drug product. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. Although the majority of misinterpretations were misspelled/phonetic variations of the proposed name, Alvesco, in the written prescription studies Alvesco was misinterpreted as Alveno, which looks similar to the over-the-counter product Aveeno when scripted (see below).

Alvesco *Aveeno*

Aveeno is an over-the-counter line of body care products manufactured by Johnson & Johnson. Aveeno products include Aveeno Soothing Bath Treatment, Aveeno Skin Relief Moisturizing Lotion, Aveeno Diaper Rash Cream, as well as others. Both Alvesco and Aveeno start with an 'A' and end with an 'o' which is the largest contributor to the look-alike characteristics of the names. Additionally, the second syllable of each name 'ves' and 'vee' are orthographically similar. However, Alvesco and Aveeno have numerous differentiating product characteristics such as the conditions of use, product strength, indication for use, frequency of administration, route of administration and dosage formulation. Therefore, the differences in the middle of each name as well as the differing product characteristics are distinguishable enough to decrease the potential for look-alike confusion between Alvesco and Aveeno.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Alvesco, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified several areas of possible improvement, which might minimize potential user error.

A. CARTON LABELING

Delete the statement ' _____' b(4)

B. INSERT LABELING

See Carton Labeling Comment.

C. PATIENT'S INSTRUCTIONS FOR USE LABELING

1. See Carton Labeling comment.
2. How To Use ALVESCO Section: Label all pictures with numbers (e.g. Figure 1) and refer to figure numbers in the instructions. (e.g., "Hold the inhaler as shown in Figure 2.")

OR

Revise the statements relating to the pictures so that the statement refers to the picture (e.g. Hold the inhaler as shown below").

3. How to use ALVESCO Section, Step 5: Revise the statement to read "Rinse your mouth with water after treatment," in order to instruct patients that rinsing their mouth with water is a necessary step and not an option.

RECOMMENDATIONS:

- A. DMETS has no objections to the use of the proprietary name Alvesco. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.
- B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.
- C. DDMAC finds the proprietary name Alvesco acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Kristina C. Arnwine, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Denise P. Toyer, PharmD
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Attachment A

Verbal	Inpatient Written	Outpatient Written
Abbasco	Alnesca	Alevno
Albesco	Alnesco	Alveno
Albesco	Alresca	Alveno
Albexo	Alresca	Alveno
Alfresco	Alresca	Alveno
Alvesco	Alresco	Alveno
Alvesco	Alresca	Alveno
Alvesco	Alresca	Alveno
Alvesco	Alresco	Alveno
Alvesco		Alveno
Alvesko		Alveno
Alvesko		Alveno
Alvesko		Alveno
Avalco		Alvero
		Alvesca
		Alvesco
		Alvesco

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/s/

Denise Toyer
3/26/04 02:51:08 PM
DRUG SAFETY OFFICE REVIEWER
Entering for Kristina Arnwine, DMETS reviewer

Carol Holquist
3/26/04 02:55:35 PM
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips
3/29/04 08:05:43 AM
DRUG SAFETY OFFICE REVIEWER