

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-929

PROPRIETARY NAME REVIEW(S)

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; White Oak 22; Mail Stop 4447)**

DATE RECEIVED: October 31, 2005	DESIRED COMPLETION DATE: May 23, 2006	ODS CONSULT #: 03-0296-2
DATE OF DOCUMENT: September 23, 2005	PDUFA DATE: July 23, 2006	

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THROUGH: Alina Mahmud, RPh, MS, Team Leader
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FROM: Jinhee Jahng, PharmD, Safety Evaluator
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PRODUCT NAME: **Symbicort**
(Budesonide and Formeterol Inhalation Aerosol)
80 mcg/ 4.5 mcg and 160 mcg/4.5 mcg

NDA#: 21-929 (IND 63,394)

NDA SPONSOR: AstraZeneca LP

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Symbicort. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. 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.
2. DMETS recommends implementation of the labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name, Symbicort, 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 Diane Smith, Project Manager, at 301-796-0538.

**Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
White Oak 22, Mail Stop 4447
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: November 7, 2005

NDA#: 21-929 (IND 63,394)

NAME OF DRUG: Symbicort (Budesonide and Formoterol Inhalation Aerosol)
80 mcg/4.5 mcg and 160 mcg/4.5 mcg

NDA HOLDER: AstraZeneca LP

I. INTRODUCTION:

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

DMETS reviewed the proposed proprietary name, Symbicort, in ODS consult #03-0296 and 03-0296-1, dated March 25, 2004 and January 26, 2005 respectively. DMETS did not recommend use of the name, Symbicort, in the first consult due to its potential look-alike and/or sound-alike similarities to Synacort, but reversed this original decision in the latter review, provided that the sponsor commit to working with the sponsor of Synacort to remove this brand name from all available reference texts. According to the Division Project Manager, the sponsor is in the process of buying the name Synacort, which also involves removing the name from all available reference texts. Further information regarding this issue will be submitted to the NDA. Thus, DMETS is basing this review on this most recent information.

PRODUCT INFORMATION

Symbicort Inhalation Aerosol contains budesonide and formoterol fumarate dihydrate. Budesonide is an anti-inflammatory corticosteroid whereas formoterol fumarate is a long-acting selective beta₂-adrenergic agonist. Symbicort is indicated for the long-term maintenance treatment of asthma in patients 12 years of age and older and is available in two strengths, 80 mcg/4.5 mcg and 160 mcg/4.5 mcg, containing budesonide and formoterol fumarate dihydrate per inhalation, respectively. Each dose is administered as two inhalations, resulting in a dose of 160 mcg/9 mcg or 320 mcg/9 mcg. Symbicort should be administered twice daily (in the morning and the evening).

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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 databases^{3,4} for existing drug names which sound-alike or look-alike to Symbicort 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 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.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Symbicort. 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 finds the proprietary name Symbicort acceptable from a promotional perspective.
2. The Expert Panel identified one additional proprietary name that was thought to have the potential for confusion with Symbicort. This product is listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

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¹ MICROMEDEX Integrated Index, 2005, 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 98-05, 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>.

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

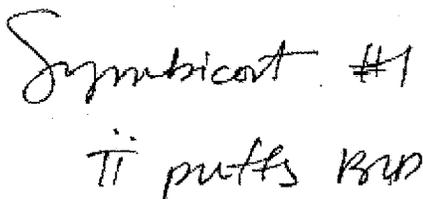
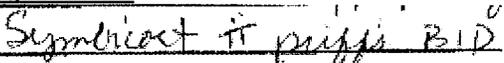
Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Symbicort	Budesonide/Formoterol Inhalation Aerosol 80 mcg/4.5 mcg and 160 mcg/4.5 mcg	Either 2 actuations twice daily of Symbicort 160 mcg /4.5 mcg or Symbicort 80 mcg/4.5 mcg depending on the severity of asthma.	
Symbyax	Fluoxetine HCl/Olanzapine Capsules 25 mg/6 mg, 25 mg/12 mg, 50 mg/6 mg, 50 mg/12 mg	1 capsule daily.	LA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. 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 Symbicort 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 120 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 Symbicort (see below). 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>Inpatient RX:</p> 	<p>Symbicort #1 2 puffs twice daily.</p>

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See appendix A for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Symbicort, the primary concerns related to look-alike confusion with Symbyax and Synacort. Based on the information provided by the sponsor concerning the name Synacort, DMETS will not consider this name in the following assessment.

Additionally, 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 of the aforementioned names. 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. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Symbicort.

Symbyax and Symbicort were found to look-alike when handwritten. Symbyax is a combination product containing olanzapine (a neuroleptic) and fluoxetine (a selective serotonin reuptake inhibitor). Symbyax is indicated for the treatment of depressive episodes associated with bipolar disorder and is usually given once daily in the evening. Symbyax comes available as 25 mg/6mg, 25 mg/12 mg, 50 mg/6 mg, and 50 mg/12 mg capsules. Symbyax and Symbicort share the identical prefix, "Symb-", but their prefixes vary ("-yax" vs. "-icort") in appearance (see writing sample below) and length (Symbyax has seven letters whereas Symbicort has nine). Although the "x" and the "t" in Symbyax and Symbicort, respectively, have the potential to look-alike, their different product characteristics help to distinguish the two names from one another. Symbyax and Symbicort differ in dosage form (capsule vs. inhalation aerosol), dosage strength (25 mg/6 mg, 25 mg/12 mg, 50 mg/6 mg, 50 mg/12 mg vs. 80 mcg/4.5 mcg, 160 mcg/4.5 mcg), and dosing schedule (once daily vs. twice daily). Therefore, DMETS believes the potential for confusion between Symbyax and Symbicort to be minimal.

Symbyax
Symbicort
■ YAX
■ ICORT

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

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

A. GENERAL COMMENTS

1. The proprietary and established names should be the most prominent information on the labels and labeling. In review of the draft labels and labeling, the established name appears to lack prominence in comparison to the other items (i.e. proprietary name, strength, graphic design, company name, etc.). Per 21 CFR 201.10(g)(2), "...the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including

typography, layout, contrast, and other printing features". Revise labels and labeling so that the established name is more prominent.

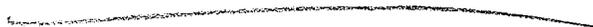
2. Two graphic designs are present on the draft labels and labeling (see below). It is unclear what the significance of these graphics are and what they represent. These graphic items appear more prominent than the proprietary and established names, whereas the names and strength should appear most prominently on the labels and labeling. Therefore, we recommend removing this graphic design or at a minimum decreasing the size so that the established and proprietary names and strength are the most prominent information on the labels and labeling.



3. Relocate the location of the net quantity statement (i.e. 60 inhalations or 120 inhalations) so that it is not in close proximity to the product strength in order to avoid confusion between the two.
4. Some of the container labels, carton and insert labeling omit the unit designation associated with the strength. Revise the labels and labeling so that the strengths are expressed with the units (i.e. 80 mcg/4.5 mcg and 160 mcg/4.5 mcg).
5. The dosage form, "inhalation aerosol" is presented in a smaller font than the established name. Revise the labels and labeling so that the font size for these two items is the same.

B. DEVICE LABEL

1. See comments A-1 and A-4.
2. The product strength is presented twice on the shield container labels (see black arrows below). Revise so that the strength appears only once.



C. CONTAINER LABEL

1. See GENERAL COMMENTS.
2. The current presentation of the established name and strength is confusing. Revise so that the label instead reads:

budesonide and formeterol fumarate dihydrate Inhalation Aerosol
160 mcg/4.5 mcg*

D. CARTON LABELING

1. See GENERAL COMMENTS.
2. Increase the prominence of the "Professional Sample – Not for Sale" statement.
3. We note that the product strength is based on formeterol **fumarate dihydrate** and not formeterol. Thus, we recommend that the labels be revised so that the established name and strength read as follows:

budesonide and formeterol fumarate dihydrate Inhalation Aerosol

4. In its current format, it is unclear whether the 80 [mcg]/4.5 mcg and 160 [mcg]/4.5 mcg describe the total contents or the amount delivered per actuation. Revise the labels to include a statement on the principal display panel that indicates the total amount of drug delivered per actuation. For example:

E. INSERT LABELING

1. See comment A-4.
2. In the DOSAGE AND ADMINISTRATION section, the instructions read
Expressing the dose in this manner may be confusing, since it is not clear what strength meter the section is referring to. Revise to clarify this statement or remove it.

F. PATIENT PACKAGE INSERT (PPI)

No comments.

G. DOSE CARD

1. In the description section on the back of the dose card, it reads "... of your morning (blue)...". The blue font color (see arrow on page 8) used for "(blue)" is difficult to read against the red background. The yellow font color is also difficult to read and DMETS recommends not using the term "Yellow Zone" to describe the refill time. For asthmatics who use peak flow meters, yellow zone is a term used to describe "caution". Revise accordingly.



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/s/

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