

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-742**

**PROPRIETARY NAME REVIEW(S)**

11/29/07

**CONSULTATION RESPONSE**

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT**

**OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY**

**(DMETS; HFD-420, White Oak Building 22, Mail Stop 4447)**

**Center for Drug Evaluation and Research**

<b>DATE RECEIVED:</b> November 2, 2007	<b>DESIRED COMPLETION DATE:</b> November 26, 2007	<b>OSE REVIEW #:</b> 2007-2293
<b>DATE OF DOCUMENT:</b> November 3, 2007	<b>PDUFA DATE:</b> November 30, 2007	

**TO:** Norman Stockbridge, M.D., Director  
Division of Cardiovascular and Renal Products

**THROUGH:** Todd Bridges, RPh, Team Leader  
Denise Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Errors and Technical Support

**FROM:** Diane C. Smith, PharmD, Safety Evaluator  
Division of Medication Errors and Technical Support

<b>PRODUCT NAME:</b> Bystolic (Nebivolol Hydrochloride) Tablets 2.5 mg, 5 mg, and 10 mg	<b>NDA SPONSOR:</b> Mylan Bertek Pharmaceuticals, Inc.
<b>NDA #:</b> 21-742	

**RECOMMENDATIONS:**

- DMETS has no objections to the use of the proprietary name, Bystolic. DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the signature date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
- DMETS does not have additional label and labeling recommendations at this time (see section III of this review).
- DDMAC finds the proprietary name, Bystolic, acceptable from a promotional perspective.

We would be willing to meet with the Division for further discussion, if needed. DMETS would appreciate feedback of the final outcome of this consult. Please copy DMETS on any correspondence forwarded to the sponsor pertaining to this review. If you have further questions or need clarifications, please contact Darrell Jenkins, OSE Project Manager, at 301-796-0558.

Division of Medication Errors and Technical Support (DMETS)  
Office of Surveillance and Epidemiology  
HFD-420; WO 22; Mail Stop 4447  
Center for Drug Evaluation and Research

PROPRIETARY NAME, LABEL AND LABELING REVIEW

DATE OF REVIEW: November 29, 2007  
NDA #: 21-742  
NAME OF DRUG: **Bystolic**  
(Nebivolol Hydrochloride) Tablets  
2.5 mg, 5 mg and 10 mg  
NDA HOLDER: Mylan Bertek Pharmaceuticals, Inc.

**I. INTRODUCTION:**

This consult was written in response to a request from the Division of Cardiovascular and Renal Products, for assessment of the proprietary name, Bystolic, regarding potential name confusion with other proprietary or established drug names. The sponsor initially submitted the proposed proprietary name, Cirmaxen, for this product. However, in OSE review 2007-1395 (dated October 18, 2007), DMETS did not recommend the use of the name Cirmaxen due its similarities in appearance to Coumadin and Aromasin when scripted. Subsequently, the sponsor submitted the names [redacted] (primary) and Bystolic (secondary) for review. However, DDMAC objected to the name [redacted] because it overstates the efficacy of the product. The Division concurred with DDMAC's objection and requested an assessment of the name Bystolic. Additionally, revised container labels and carton labeling were submitted for review and comment at this time.

PRODUCT INFORMATION

Bystolic is a competitive and selective  $\beta_1$ -adrenergic (cardioselective) receptor antagonist indicated in the management of hypertension. The usual dose is 5 mg to 10 mg once daily. Bystolic will be supplied as 2.5 mg, 5 mg and 10 mg oral tablets and packaged in cartons of 100 count (10 strips of 10 unit dose tablets) and bottles of 30, 100 [redacted] count.

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## II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of the internet, several standard published drug product reference texts<sup>1,2</sup> as well as several FDA databases<sup>3,4</sup> for existing drug names which sound-alike or look-alike to Bystolic 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 conducted<sup>5</sup>. The Saegis<sup>6</sup> 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 inpatient prescription studies and a 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 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, Bystolic. 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 proposed proprietary name, Bystolic, acceptable from a promotional perspective.
2. The Expert Panel identified eight names that were thought to have the potential for confusion with Bystolic. They are Byetta, Vytorin, Myfortic, Bistort, Byclomine, Betoptic, Bisacodyl and Bestolic. Additionally, the panel identified two medical terms, systolic and diastolic, that were thought to have potential for confusion with Bystolic.

<sup>1</sup> 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.

<sup>2</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> 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.

<sup>4</sup> Phonetic and Orthographic Computer Analysis (POCA)

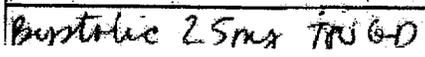
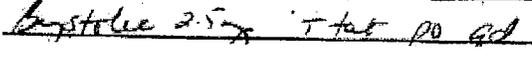
<sup>5</sup> WWW location <http://www.uspto.gov/tmdb/index.html>.

<sup>6</sup> Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at [www.thomson-thomson.com](http://www.thomson-thomson.com)

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 Bystolic with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten orders or verbal pronunciation of the drug name. These studies employed a total of 122 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. Two inpatient orders were written, consisting of a combination of marketed and unapproved drug products and an order for Bystolic (see below). These orders were optically scanned and delivered to a random sample of the participating health professionals via e-mail. In addition, the 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 ORDERS	VERBAL PRESCRIPTION
<p data-bbox="302 856 461 884"><u>Inpatient RX 1:</u></p> 	<p data-bbox="862 863 1068 890"><u>Verbal Prescription:</u></p> <p data-bbox="862 926 1057 953">Bystolic 2.5 mg</p> <p data-bbox="862 961 911 989">#30</p> <p data-bbox="862 997 1143 1024">1 tablet by mouth daily</p>
<p data-bbox="302 999 461 1026"><u>Inpatient RX 2:</u></p> 	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. Appendix A (page 6) contains a complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

Upon review of the product, Bystolic for name confusion, eight names were identified as potential look and/or sound alike to Bystolic: Byetta, Vytorin, Myfortic, Bistort, Byclomine, Betoptic, Bisacodyl, and Bestolic. Additionally, the medical terms systolic and diastolic were identified as having a similarity to Bystolic.

DMETS also conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name Bystolic, could be confused with any of the aforementioned names. The majority of interpretations were misspelled/phonetic variations of the proposed name, Bystolic.

Upon initial analysis of the eight names identified as being potentially similar in sound and/or appearance, we determined that none of the eight names would be considered further for the reasons outlined below:

- In addition to lacking orthographic and/or phonetic similarities with Bystolic, Byetta, Vytorin, Myfortic, Bistort, Betoptic, and Bisacodyl do not share product commonalities such as dosage form, route of administration, product strength, usual dose, indication of use, duration of usage, prescriber population, dosing units, context of use and/or prescription only status.
- Byclomine was not reviewed further due to discontinuation of the product along with the fact that there are no generic products available.
- Bestolic is a proprietary name that is owned by Forest Laboratories but has never been submitted to the Agency as a proposed name for any application. Additionally, Bestolic does not appear to be attached to any specific drug product.

Similarly, the terms systolic and diastolic were not considered further because we can not foresee a clinical situation where either of these terms would be confused with the proposed name.

Thus, DMETS finds the name Bystolic acceptable.

### **III. LABELING, PACKAGING , AND SAFETY RELATED ISSUES:**

In review of the revised container labels and carton labeling of Bystolic, DMETS focused on human factors and safety issues relating to medication errors. DMETS acknowledges that the sponsor has addressed all of our label and labeling recommendations made in OSE review 2007-1395, dated October 18, 2007. We do not have any additional comments at this time.

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### Appendix A

Voice	Inpatient #1	Inpatient #2
Bistolic	Bystolic	Bystolic
Bicelux	Bystolic	Bystolic
Biselect	Bystobic	Bystolie
Basalic	Bystolic	Bystolie
	Bystolic	Bystoic
	Bystolic	Bystolic
	Bystolic	Bystolic
	Bystolic	Bystolic
	Bystolic	Bystolie or Bystolic
	Bystolic	Bystole
	Bystolic	Bystolic
		Bystolie
		Bystolic

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/s/

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Diane Smith  
11/29/2007 01:45:50 PM  
CSO

Todd Bridges  
11/29/2007 03:04:27 PM  
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung  
11/29/2007 03:32:32 PM  
DRUG SAFETY OFFICE REVIEWER  
Also signing for Carol Holquist

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