

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-866

OTHER REVIEW(S)

Division of Metabolism and Endocrinology Products

PROJECT MANAGER LABELING REVIEW

Application Number: 20-866

Drug Name: Cycloset (bromocriptine mesylate) 0.8 mg Tablets

Sponsor: VeroScience

Material Reviewed: Draft package insert in FPL, Carton & Container labels, Patient Counseling Information (as part of PLR)

Submission Date (AZ): April 13, 2008

Receipt Date: April 15, 2008

Reviewed by: Jena Weber, Regulatory Project Manager

Indication: This new drug application provides for the use of Cycloset as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Background and Summary Description:

NDA 20-866 was originally submitted by Ergoscience on August 18, 1997. A not approvable letter was issued on November 20, 1998. This communication contained specific efficacy and safety deficiencies as outlined in FDA reviews.

A major amendment was submitted on April 15, 1999, from Ergo Research Corporation. FDA issued an approvable letter on October 15, 1999, requesting additional safety data, pharmacology/toxicology, and biopharmaceutical data.

A major amendment from VeroScience dated April 13, 2008, was received and included a response to all outstanding deficiencies.

Review:

Note: Proprietary name found acceptable (review #3) by DMEPA on April 7, 2009.

Carton and Container Labels: Submitted December 26, 2008. These found acceptable on January 30, 2009 (see DMEPA review).

Patient Labeling: Recommendations considered and labeling revisions made as per consult review from DDMAC dated February 9, 2009.

Patient Labeling: Recommendations considered and labeling revisions inserted as per consult review from DRISK dated January 29, 2009.

Package Insert Labeling: Acceptable as per May 1, 2009, submission.

Conclusions: NDA should be approved, FPL is acceptable, submit in SPL.

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/s/

Jena Weber
5/5/2009 02:41:48 PM
CSO



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: January 30, 2009

To: Mary Parks, MD, Director
Division of Metabolism and Endocrinology Products

Thru: Denise Toyer, PharmD, Deputy Director
Division of Medication Error Prevention and Analysis

From: Melina Griffis, R.Ph, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name: Cycloset (Bromocriptine Mesylate) Tablet 0.8 mg

Application Type/Number: NDA 20-866

Applicant: VeroScience

OSE RCM #: 2008-811

1 INTRODUCTION

The Division of Medication Error Prevention and Analysis (DMEPA) completed a labeling review for Cycloset (OSE RCM #2008-811) on December 15, 2008 in which we made one recommendation regarding the proposed container labels. In a submission dated December 26, 2008, the Applicant submitted their revisions addressing DMEPA's requested change.

2 MATERIAL REVIEWED

DMEPA reviewed our previous labeling review for Cycloset (OSE review #2008-811 dated December 15, 2008) and we also reviewed the revised labels submitted by the Applicant dated December 26, 2008. See Appendix A for pictures of the labels.

3 DISCUSSION

The Applicant has changed the container labels according to our recommendations and we have no further comments.

4 CONCLUSIONS AND RECOMMENDATIONS

The Applicant has satisfactorily revised the labels per our December 15, 2008 request.

If you have further questions or need clarifications, please contact Mildred Wright, OSE Project Manager, at 301-796-1027.

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 Trade Secret / Confidential (b4)

 ✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Melina Griffis
1/30/2009 02:05:14 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
1/30/2009 02:56:05 PM
DRUG SAFETY OFFICE REVIEWER



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: January 29, 2009

To: **Mary Parks, M.D., Director**
Division of Metabolism and Endocrinology Products

Through: **Jodi Duckhorn, M.A. Team Leader**
Patient Labeling and Education Team
Division of Risk Management

From: **Nancy Carothers, RN**
Patient Product Information Reviewer
Patient Labeling and Education Team
Division of Risk Management

Subject: **DRISK Review of Patient Labeling (Patient
Package Insert)**

Drug Name(s): **CYCLOSET (Bromocriptine Mesylate) Tablets**

**Application
Type/Number:** **NDA 20-866**

Applicant/sponsor: **VeroScience LLC**

OSE RCM #: **2008-811**

1 INTRODUCTION

CYCLOSET™ Bromocriptine Mesylate Tablets is a prescription medicine used with diet and exercise to improve glycemic control in patients with type 2 diabetes. CYCLOSET can be used alone or as an adjunctive therapy with other type 2 diabetes therapies. A resubmission of labeling information was submitted in response to FDA comments of October 9, 2008, and during this review process there was a delay in obtaining a substantially complete Professional Information (PI) until inspections were completed at the end of 2008. The inspections were completed in December 2008. The Division of Metabolism and Endocrinology Products requested that the Division of Risk Management's Patient Labeling and Education Team review the Patient Package Insert. This review is written in response to that request.

2 MATERIAL REVIEWED

- CYCLOSET™ *Professional Information* (PI) submitted on April 13, 2008 and revised by the Review Division throughout the current review cycle and provided to DRISK on December 31, 2008.
- CYCLOSET™ *Patient Package Insert* (PPI) submitted on April 13, 2008 and revised by the Review Division throughout the current review cycle and provided to DRISK on December 31, 2008.

3 DISCUSSION

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The *Patient Package Insert* submitted by the sponsor has a Flesch Kinkaid grade level of 8.2, and a Flesch Reading Ease score of 56.9%. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level).

In our review of the *Patient Package Insert*, we have:

- simplified the wording and clarified concepts where possible,
- ensured that the PPI is consistent with the PI,
- removed unnecessary and redundant information,
- ensured that the PPI meets the criteria as specified in the FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APFont to make medical information more accessible for patients with low vision. We have reformatted the PPI document using the font APFont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the PPI. Comments to the review division are **bolded, underlined, and italicized**.

We are providing the review division a marked-up and clean copy of the revised PPI. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the PPI.

4 CONCLUSIONS AND RECOMMENDATIONS

- In the section, "Who should not take CYCLOSET?":
 - we included "patients with an allergy to the active ingredient bromocriptine or to any of the other ingredients in CYCLOSET". The RD should clarify whether this is a real or theoretical allergic reaction

to CYCLOSET. A description of an allergic reaction to CYCLOSET does not appear under Warnings and Precautions, Adverse Events, or any section of the PI except in Contraindications.

- we included “patients who are breastfeeding”. This contraindication is explained in the post marketing section (6.2) of the PI for the active ingredient (bromocriptine) but it is not explained in the Contraindications section, Nursing Mothers section (8.3), or in Patient Counseling, (although it is mentioned in these sections). We defer to the RD as to whether this contraindication is for this specific drug product and whether it should appear in other sections of the PI with further explanation.
- the sponsor’s proposed PPI included Type 1 diabetes mellitus and Diabetic ketoacidosis. We have moved these two conditions to the section: “What should I tell my healthcare provider before taking CYCLOSET?”. The “Who should not take CYCLOSET?” section of the PPI should be limited to only those conditions listed in the PI as Contraindications.
- the sponsor’s draft PPI included a contraindication for “during pregnancy” and when using “dopamine antagonists.” We have moved these to “What should I tell my healthcare provider before taking CYCLOSET?” and “Tell your healthcare provider about all the medicines you take...” respectively because they are not listed as contraindications in the PI. The “Who should not take CYCLOSET?” section of the PPI should be limited to only those conditions listed in the PI as Contraindications.
- In the section “What should I tell my healthcare provider before taking CYCLOSET?”:
 - we added Type 1 diabetes mellitus and Diabetic ketoacidosis for the reasons explained above.
 - we added “have migraine headaches” because syncopal migraines are contraindicated and the type of migraine should be assessed by the healthcare provider.
 - we added “have or have had a mental health condition, especially a psychotic disorder” because CYCLOSET is not recommended for patients with a severe psychotic disorder. It may exacerbate the condition and may decrease the effectiveness of treatment for this disorder. The healthcare provider should assess whether the condition is severe or not.
 - we removed references _____ that were included in the sponsor’s proposed PPI. This _____ is not mentioned in the PI. If the information is to be included in the PPI, then it must be added to the PI. The PI and PPI must be consistent.
- In the section, “Tell your healthcare provider about all the medicines you take,”:
 - we have instructed patients to tell their healthcare provider about medicines taken for mental health conditions (especially anti-psychotic medicines), migraine or other types of headaches, and for type 2 diabetes. These conditions have been added here because under “Drug Interactions” (See 5.4 and 7.0), the PI advises that CYCLOSET is a dopamine agonist and therefore may diminish the effectiveness of dopamine antagonists (anti-psychotic treatment). Also, ergot-related medicines are contraindicated and CYCLOSET is sometimes given with other type 2 diabetes medicines.
 - The PI says that CYCLOSET may interact with “highly protein-bound” drugs but it does not describe the seriousness of this interaction. We defer to the RD as to whether this group of drugs should be added to the bulleted list in this section of the PPI.

b(4)

We do not recommend providing a partial list of drug names. If all drugs in a class are not listed, patients may incorrectly assume that if a drug is not listed, it is not a problem.

- In the section, “What are the possible side effects of CYCLOSET?”:
 - we added the following as serious side effects: “low blood pressure, sweating, fainting, and severe dizziness which can be caused by postural hypertension. This happens when your blood pressure lowers rapidly after you stand up from a lying down position.” These side effects have been added because they are listed in the “Warnings and Precautions” and “Patient Counseling” sections of the PI.
 - we added “low blood sugar” as a common side effect. Low blood sugar occurred in 8.6% of CYCLOSET-treated patients versus 5.2% of placebo-treated patients in one trial (See 6.1). Also, the

Patient Counseling section says to inform patients of the importance in managing hypoglycemia and hyperglycemia.

- We have added the following statement to the end of the section, “What are the possible side effects of CYCLOSET?”:

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

This verbatim statement is required for all Medication Guides. Although not required for voluntary PPIs like CYCLOSET, we recommend adding this language to all FDA-approved patient labeling for consistency.

- _____ was included in the sponsor’s proposed PPI. This disease-specific information detracts from the product-specific information. It can be placed at the end of the PPI or, preferably, it can be addressed with patients separately from the product-specific information. **b(4)**

Please let us know if you have any questions.

8 Page(s) Withheld

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✓ Draft Labeling (b4)

 Draft Labeling (b5)

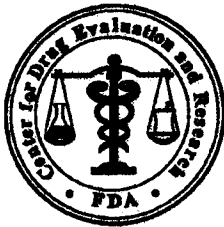
 Deliberative Process (b5)

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/s/

Nancy B Carothers
1/29/2009 03:53:46 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
1/29/2009 04:01:58 PM
DRUG SAFETY OFFICE REVIEWER



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: December 15, 2008

To: Mary Parks, MD
Director, Division of Metabolism and Endocrinology Products

Thru: Kellie Taylor, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Melina Griffis, R.Ph, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Cycloset (Bromocriptine Mesylate) Tablet 0.8 mg

Application Type/Number: NDA 20-866

Applicant/sponsor: VeroScience

OSE RCM #: 2008-811

1 INTRODUCTION

This memorandum is in response to a request from the Division of Metabolism and Endocrinology Products for a review of the Applicant's submissions dated October 9, 2008 and November 12, 2008 which provided revised container labels and insert labeling in response to recommendations outlined in OSE review #2008-811 dated September 26, 2008.

1.1 REGULATORY HISTORY

Cycloset is a pending NDA and to date the Division of Metabolism and Endocrinology Products has not issued an official action in response to the resubmission dated April 15, 2008. Cycloset is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. DMEPA found the name, Cycloset, acceptable in OSE review #2008-811 dated September 26, 2008. At that time, DMEPA also reviewed the sponsor's container labels and insert labeling and provided recommendations.

2 MATERIAL REVIEWED

DMEPA reviewed the Applicant's revised container labels and insert labeling submitted October 9, 2008 and November 12, 2008.

3 DISCUSSION

Based upon our assessment of the labels and labeling, the Division of Medication Error Prevention and Analysis acknowledges that all but one concern outlined in OSE review #2008-811, dated September 26, 2008 have been addressed and that the proposed labels (see Appendix A) are consistent with our recommendations.

However, as previously recommended DMEPA continues to have concerns with the size of the company name and logo on the container labels. As currently displayed the size of the company name and logo, "Veroscience", is of similar size and prominence compared to the proprietary name and strength. The proprietary name, established name and strength should be the most prominent information on the label. In addition, the company name and logo should be relocated to the bottom of the principle display panel which is a less prominent area.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA continues to recommend that the company name and logo be decreased in size and prominence so that it does not compete with the drug name and strength of the product. We have provided recommendations in Section 5 and request this information be forwarded to the Applicant.

The Division of Medication Error Prevention would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy our division on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Cheryl Campbell, Project Manager, at 301-796-0723.

5 COMMENTS TO THE APPLICANT

- 1. We continue to have concerns with the size of the company name and logo on the container labels. As currently displayed the size of the company name and logo, "Veroscience", is of similar size and prominence compared to the proprietary name and strength and should be decreased so that it does not compete with the proprietary and established names and strength. Revise so that the company name and logo is relocated to the bottom of the principle display panel which is a less prominent area.**

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 ✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Melina Griffis
12/15/2008 07:04:27 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
12/15/2008 07:53:18 AM
DRUG SAFETY OFFICE REVIEWER



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: December 8, 2008

To: Mary Parks, MD
Director, Division of Metabolism and Endocrinology Products

Thru: Kellie Taylor, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

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 Trade Secret / Confidential (b4)

 ✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 15, 2008

TO: Mary H. Parks, MD
Director,
Division of Metabolism and Endocrinology Products
(DMEP)

FROM: Gopa Biswas, Ph.D.
Staff Fellow
Division of Scientific Investigations

THROUGH: C.T. Viswanathan, Ph.D. *Mart K. Yan 10/15/08*
Associate Director - Bioequivalence
Division of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 20-866, Cycloset™
(bromocryptine mesylate) Tablets, 0.8mg Sponsored by
Veroscience LLC

At the request of DMEP, the Division of Scientific Investigations (DSI) audited the following bioequivalence study:

Study Number: BON-P6-262 (Clinical Project Code)

Study Title: "Single Dose Crossover Comparative Bioavailability Study of Bromocriptine Mesylate 0.8 mg Tablets Following Administration of a 4.8 mg Dose in Healthy Male and Female Volunteers/Fed State"

The clinical portion of the Study BON-P6-262 was conducted at Algorithm Pharma Inc., Mount-Royal, Quebec, Canada and the analytical portion of the study was conducted at _____

Based on inspectional history of _____
the referenced site was not inspected.

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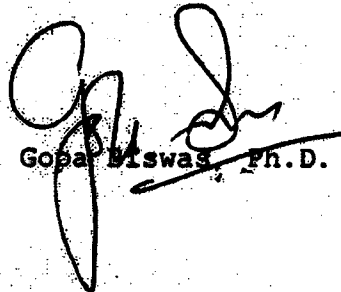
Following the inspection at Algorithm Pharma Inc (September 2-5, 2008), Form FDA-483 was not issued and no significant findings were identified for Study BON-P6-262.

Page 2 - NDA 20-866, Cycloset™ (bromocryptine mesylate) Tablets,
0.8mg

Conclusion:

Following the above inspection, DSI recommends that the clinical data from Study BON-P6-262 be accepted for review.

After you have reviewed this memo, please append it to the original NDA submission.


Gopal Biswas, Ph.D. 10/15/08

Final Classification:

NAI: Algorithme Pharma Inc., Mount-Royal, Quebec, Canada

cc:

HFD-45/Vaccari

HFD-48/Biswas/Patague/CF

OND/ODEII/DMEP/Weber

HFR-SW2500/Mussawir-Bias

Draft: GB

Edit: SS

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FACTS

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/s/

Gopa Biswas

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Hard copy signed by Dr Yau for Dr Viswanathan