

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-866

PROPRIETARY NAME REVIEW(S)



**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: April 7, 2009

To: Mary Parks, M.D., Director
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Subject: Proprietary Name Review

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

Application Type/Number: NDA 20-866

Applicant: VeroScience

OSE RCM #: 2008-1940

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

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EXECUTIVE SUMMARY

The proposed proprietary name, Cycloset, was previously reviewed by DMEPA in 2008 (OSE review 2008-811 dated 9/26/2008 and 2008-1940 dated 12/18/2008) without objection. Since those reviews none of the product characteristics have been revised. We identified six new names for their similarity to Cycloset and the results of the Proprietary Name Risk Assessment found that the proposed name, Cycloset, is not vulnerable to name confusion that could lead to medication errors. Thus, the Division of Medication Error Prevention and Analysis does not object to the use of the proprietary name, Cycloset, for this product. This is considered a final review, however, if approval is delayed beyond 90 days from the date of this review, the proprietary name should be resubmitted for re-review.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Metabolism and Endocrinology Products for an assessment of the proposed proprietary name, Cycloset, regarding potential name confusion with other proprietary or established drug names in the usual practice setting. Container labels, carton and insert labeling were also provided to be evaluated from a medications errors perspective. DMEPA reviewed the label and labeling in conjunction with the proprietary name review (see OSE review 2008-811 dated 9/26/2008).

1.2 PRODUCT INFORMATION

Cycloset is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. It is available in one strength, 0.8 mg tablets, and the recommended dose of Cycloset is 1.6 mg to 4.8 mg (two to six tablets) to be taken once daily within two hours of waking.

Bromocriptine mesylate is also marketed under the proprietary name Parlodel® as an oral tablet available in 2.5 mg and 5 mg. Generic equivalent products also exist but do not have a proprietary name.

2 METHODS AND MATERIALS

This section describes the methods and materials used by the Division of Medication Error Prevention and Analysis conducting a Proprietary Name Risk Assessment. The primary focus of the assessment is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.¹

2.1 PROPRIETARY NAME RISK ASSESSMENT

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name, Cycloset, and the proprietary and established names of drug products existing in the marketplace and those pending IND, BLA, NDA, and ANDA products currently under review by the Center.

For the proprietary name, Cycloset, the DMEPA staff a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Sections 2.1.1 for detail) and held an

¹ National Coordinating Council for Medication Error Reporting and Prevention.
<http://www.nccmerp.org/about/MedErrors.html>. Last accessed 10/11/2007.

CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see 2.1.1.2). The Division of Medication Error Prevention and Analysis also conducts internal CDER prescription analysis studies (see 2.1.2), and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment (see detail 2.1.4). In this case, an internal CDER prescription analysis study was conducted in OSE Review #2008-811, and was therefore not repeated for this review.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see detail 2.1.4). The overall risk assessment is based on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors.

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.² FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. The Division of Medication Error Prevention and Analysis uses the clinical expertise of the medication error staff to anticipate the conditions of the clinical setting that the product is likely to be used in based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap, or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. As such, the DMEPA staff considers the product characteristics associated with the proposed drug throughout the risk assessment, since the product characteristics of the proposed name may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the proposed product, the proposed indication, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, DMEPA staff considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.³

2.1.1 Search Criteria

The DMEPA Staff considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted as outlined in Appendix A.

For this review, particular consideration was given to drug names beginning with the letter 'C' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.^{4,5}

² Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

³ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

⁴ Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at <http://www.ismp.org/Tools/confuseddrugnames.pdf>

⁵ Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

To identify drug names that may look similar to Cycloset, the staff also consider the other orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (eight letters), upstrokes (three, capital letter 'C', lower case 'l' and 't'), downstrokes (lowercase 'y'), cross-strokes (lower case 't'), and dotted letters (none). Additionally, several letters in Cycloset may be vulnerable to ambiguity when scripted, including the letter 'C' may appear as 'A', 'O', 'F' or 'G'; lower case 'o' may appear as a lower case 'e' or 'a' and lower case 't' may appear as 'b'. As such, the Staff also considers these alternate appearances when identifying drug names that may look similar to Cycloset.

When searching to identify potential names that may sound similar to Cycloset, DMEPA staff search for names with similar number of syllables (three), stresses (Cy-CLO-set or Cy-clo-SET), and placement of vowel and consonant sounds. The medication error staff also considers other variations where the 'Cy' sound may be interpreted as 'Si'. The sponsor's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

DMEPA also consider the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting. For this review, the staff were provided with the following information about the proposed product: the proposed proprietary name (Cycloset), the established name (bromocriptine mesylate quick release), proposed indication (as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes), strength (0.8 mg), dose (2-6 tablets), frequency of administration (daily within two hours of waking), route (oral) and dosage form of the product (tablet). Appendix A provides a more detailed listing of the product characteristics DMEPA staff generally take into consideration.

Lastly, the DMEPA staff also considers the potential for the proposed name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. As such, these broader safety implications of the name are considered and evaluated throughout this assessment and the DMEPA staff provides additional comments related to the safety of the proposed name or product based on their professional experience with medication errors.

2.1.1.1 Database and Information Sources

The proposed proprietary name, Cycloset, was provided to the DMEPA staff to conduct a search of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to Cycloset using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 7. To complement the process, the DMEPA staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the DMEPA staff review the United States Adopted Names (USAN) stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

2.1.1.2 CDER Expert Panel Discussion

An Expert Panel Discussion is held by DMEPA to gather CDER professional opinions on the safety of the product and the proprietary name, Cycloset. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of the Division of Medication Error Prevention and Analysis (DMEPA) staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC).

The pooled results of the DMEPA staff were presented to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

2.1.2 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1.1, the primary Safety Evaluator applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Mode and Effects Analysis and provide an overall risk of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.⁶ When applying FMEA to assess the risk of a proposed proprietary name, the Division of Medication Error Prevention and Analysis seeks to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to look- or sound-alike drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is not yet marketed, the Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Appendix A. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, expert panel evaluation, and studies, and identifies potential failure modes by asking:

“Is the name Cycloset convincing similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?”

An affirmative answer indicates a failure mode and represents a potential for Cycloset to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names possess similarity that would cause confusion at any point in the medication use system and the name is eliminated from further review.

In the second stage of the Risk Assessment, all potential failure modes are evaluated to determine the likely effect of the drug name confusion, by asking

“Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?”

The answer to this question is a central component of the Safety Evaluator’s overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would ultimately not be a source of medication errors in the usual practice setting, the name is eliminated from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend that an alternate proprietary name be used. In rare instances, the FMEA findings may provide other risk-reduction strategies, such as product reformulation to avoid an overlap in strength or an

⁶ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

alternate modifier designation may be recommended as a means of reducing the risk of medication errors resulting from drug name confusion.

DMEPA will object to the use of proposed proprietary name when the one or more of the following conditions are identified in the Safety Evaluator's Risk Assessment:

1. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].
2. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
4. The proposed proprietary name contains an USAN stem, particularly in a manner that is contradictory to the USAN Council's definition.
5. DMEPA identifies a potential source of medication error within the proposed proprietary name. The proprietary name may be misleading, or inadvertently introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug name and another drug product.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, we will provide a contingency objection based on the date of approval: whichever product is awarded approval first has the right to the use of the name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

If none of these conditions are met, then DMEPA will not object to the use of the proprietary name. If any of these conditions are met, then we will object to the use of the proprietary name. The threshold set for objection to the proposed proprietary name may seem low to the Applicant; however, the safety concerns set forth in criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the Institute of Medicine, the World Health Organization, the Joint Commission on Accreditation of Healthcare Organizations, and the Institute of Safe Medication Practices, have examined medication errors resulting from look- or sound-alike drug names and called for Regulatory Authorities to address the issue prior to approval.

Furthermore, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, can be identified and remedied prior to approval to avoid patient harm.

Additionally, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational efforts and so on are low-leverage strategies that have proven to have limited effectiveness at alleviating the medication errors involving drug name confusion. Higher-leverage strategies, such as drug name changes, have been undertaken in the past; but at great financial cost to the Applicant, and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for the approving the error-prone proprietary name. Moreover, even after Applicants have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioner's

vocabulary, and as such, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval (see limitations of the process).

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the FMEA process is used to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name, and so DMEPA may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

The searches yielded a total number of 24 names as having some similarity to the name Cycloset.

Nineteen names were thought to look like Cycloset, which include: Cyclessa, Cyclinex-1 Powder, Cyclinex-2 Powder, Glyset, Cyclogyl, Cyclaine, Cyclocort, Cyclotab, Cycloserine, Cyclease, Cyclofem, Cyclogest, Enulose, Evalose, Cyankokit, Cylert, Oxytrol, Cytotec, and _____ The remaining five names _____, Cyclo-cell, Cyclosa, Cycloson and Ciclosol were thought to look and sound similar to Cycloset.

b(4)

Additionally, the Division of Medication Error Prevention and Analysis did not identify any United States Adopted Names (USAN) stems in the name Cycloset, as of the last date searched on March 27, 2009.

3.1.2 Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by DMEPA staff (see section 3.1.1. above) and noted no additional names thought to have orthographic or phonetic similarity to Cycloset.

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name.

3.1.3 Safety Evaluator Risk Assessment

Independent searches by the primary Safety Evaluator resulted in no additional names which were thought to look or sound similar to Cycloset and represent a potential source of drug name confusion.

Eighteen of the 24 names (Cyclessa, Cyclinex-1 Powder, Cyclinex-2 Powder, Glyset, Cyclogyl, Cyclaine, _____, Cyclotab, Cycloserine, Cyclease, Cyclo-cell, Cyclogest, Cyanokit, Cylert, Oxytrol, Cytotec, and _____) identified in the database searches were previously reviewed in the two previous Cycloset proprietary name review (OSE # 2008-811 and 2008-1940). Cycloset has not undergone any product characteristic changes since the previous review therefore these names did not undergo further analysis in this review.

b(4)

Six names were analyzed to determine if drug names could be confused with Cycloset and if the drug name confusion could likely result in a medication error.

Failure mode and effect analysis (FMEA) was then applied to determine if the proposed name could potentially be confused with any of the 6 names and lead to medication errors. This analysis determined

that the name similarity between Cycloset and the identified names was unlikely to result in medication errors with any of the 6 products identified for the reason presented in Appendices B and C.

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

Six names were evaluated for their potential similarity to the proposed name, Cycloset. The FMEA indicates that the proposed name is not likely to result in name confusion that could lead to medication errors.

5 CONCLUSIONS AND RECOMENDATION

The Proprietary Name Risk Assessment findings indicate that the proposed name, Cycloset, is not vulnerable to name confusion that could lead to medication errors. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Cycloset, for this product at this time. Additionally, DDMAC does not object to the proposed name, Cycloset from a promotional perspective.

However, if any of the proposed product characteristics as stated in this review are altered prior to approval of the product, DMEPA rescinds this Risk Assessment finding and the name must be resubmitted for review. In the event that our Risk Assessment finding is rescinded, the evaluation of the name on resubmission is independent of the previous Risk Assessment, and as such, the conclusions on re-review of the name are subject to change. If the approval of this application is delayed beyond 90 days from the signature date of this review, the proposed name must be resubmitted for evaluation.

We 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 us on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Mildred Wright, at 301-796-1027.

6 REFERENCES

1. *OSE reviews 2008-1236 and 2008-257. December 8, 2008 and April 11, 2008 respectively.*
2. *Micromedex Integrated Index (<http://csi.micromedex.com>)*

Micromedex contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

3. *Phonetic and Orthographic Computer Analysis (POCA)*

POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. 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. Likewise, an orthographic algorithm exists which operates in a similar fashion. This is a database which was created for the Division of Medication Error Prevention and Analysis, FDA.

4. *Drug Facts and Comparisons, online version, St. Louis, MO (<http://factsandcomparisons.com>)*

Drug Facts and Comparisons is a compendium organized by therapeutic course; contains monographs on prescription and OTC drugs, with charts comparing similar products.

5. AMF Decision Support System [DSS]

DSS is a government database used to track individual submissions and assignments in review divisions.

6. Division of Medication Errors Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

7. Drugs@FDA (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and "Chemical Type 6" approvals.

8. Electronic online version of the FDA Orange Book (<http://www.fda.gov/cder/ob/default.htm>)

Provides a compilation of approved drug products with therapeutic equivalence evaluations.

9. U.S. Patent and Trademark Office (<http://www.uspto.gov>)

Provides information regarding patent and trademarks.

10. Clinical Pharmacology Online (www.clinicalpharmacology-ip.com)

Contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. Provides a keyword search engine.

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

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

12. Natural Medicines Comprehensive Databases (www.naturaldatabase.com)

Contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

13. Stat!Ref (www.statref.com)

Contains full-text information from approximately 30 texts. Includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology and Dictionary of Medical Acronyms Abbreviations.

14. USAN Stems (<http://www.ama-assn.org/ama/pub/category/4782.html>)

List contains all the recognized USAN stems.

15. Red Book Pharmacy's Fundamental Reference

Contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

16. *Lexi-Comp* (www.lexi.com)

A web-based searchable version of the Drug Information Handbook.

17. *Medical Abbreviations Book*

Contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

DMEPA staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. The Division of Medication Error Prevention and Analysis also compare the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. DMEPA staff also examine the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly *and* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has led to medication errors. DMEPA staff apply their expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (i.e. "T" may look like "F," lower case 'a' looks like a lower case 'u,' etc), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see detail in Table 1 below). Additionally, since verbal communication of medication names is common in clinical settings, the Medication Error Staff compare the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, the Division of Medication Error Prevention will consider the Applicant's intended pronunciation of the proprietary name. However, because the Applicant has little control over how the name will be spoken in practice, the Division of Medication Error Prevention and Analysis also considers a variety of pronunciations that could occur in the English language.

Table 1. Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name

Type of similarity	Considerations when searching the databases		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	<ul style="list-style-type: none"> Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstrokes Downstrokes	<ul style="list-style-type: none"> Names may look similar when scripted, and lead to drug name confusion in written communication

		Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	<ul style="list-style-type: none"> • Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B: Proprietary names of products marketed in a Foreign Country

Proprietary Name	Country
Cyclofem	Indonesia
Cyclosa	Germany
Cycloson	Hong Kong
Ciclosol	Switzerland

Appendix C: Products with no overlap in strength and usual dosage

Product name with potential for confusion	Strength	Usual Dose (if applicable)
Cycloset (bromocriptine mesylate)	0.8 mg	1.6 mg to 4.8 mg (2 to 6 tablets) once daily in AM
Enulose (lactulose)	10 gm/15 mL solution	2 to 3 tablespoons 3 to 4 times daily
Evalose (lactulose)	10 gm/15 mL solution	2 to 3 tablespoons 3 to 4 times daily

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/s/

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**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 18, 2008

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

Through: Kellie Taylor, Pharm D., MPH, Team Leader
Carol Holquist, R.Ph. Director
Division of Medication Error Prevention and Analysis

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

Subject: Final Review

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

Application Type/Number: NDA 20-866

Applicant/sponsor: VeroScience

OSE RCM #: 2008-1940

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

1 INTRODUCTION

This memorandum is in response to a request from the Division of Metabolism and Endocrinology Products for final review of the proprietary name, Cycloset. This name was last reviewed on September 26, 2008 and found to be acceptable (see OSE review 2008-811) but a review is necessary since more than 90 days have passed since the date of our last review.

1.1 PRODUCT DESCRIPTION

Cycloset (bromocriptine mesylate quick release) is a pending NDA with an anticipated action date of January 15, 2009. This application is a re-submission in response to an approvable letter issued by the Agency on October 15, 1999. Cycloset is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. It is available in one strength, 0.8 mg tablets, and the recommended dose of Cycloset is 1.6 mg to 4.8 mg (two to six tablets) to be taken once daily within two hours of waking.

Bromocriptine mesylate is also marketed under the proprietary name Parlodel® as an oral tablet available in 2.5 mg and 5 mg. Generic equivalent products also exist but do not have a proprietary name.

2 DISCUSSION

During our final review of the proposed proprietary name, Cycloset, DMEPA identified 10 names not previously reviewed in OSE review 2008-811 (listed Appendix A) and we determined that the 10 identified names were unlikely to result in medication errors with Cycloset. Therefore, we have concluded that the proprietary name Cycloset is acceptable for this product.

3 CONCLUSIONS AND RECOMMENDATIONS

We have completed our review of the proposed proprietary name, Cycloset, and have concluded that it is acceptable. However, if the product approval is delayed beyond 90 day from the date of this memo, the proposed name must be resubmitted for evaluation.

The Division of Medication Errors 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 us on any communication to the sponsor with regard to this review. If you have further questions or need clarifications, please contact Cheryl Campbell, project manager, at 301-796-0723.

Appendix A: Additional names identified and reason to discard

Cyclostad (acyclovir)	Marketed in Phillipines
Cyclocen (dicyclomine) 20 mg IV	Different dose and route of administration
Cyclo-cell	Marketed in Germany
Cyclomed	Marketed in Israel
Cyclogest	International brand for progesterone
Cyclocide	International brand for cytarabine
Ocucoat (hydroxypropylmethylcellulose)	Different route, dose and setting of use (used as an ophthalmic surgical aid)
Cyanokit (hydroxocobalamine injection, 2.5 g per vial)	Different dose and route of administration
Oxytrol (oxybutynin transdermal system; 39 cm ² system)	Different dose and route of administration
_____	Product withdrawn; no generics available

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/s/

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**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: September 26, 2008

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

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

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

Subject: Proprietary Name, Label and Labeling Review

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

Application Type/Number: NDA 20-866

Applicant/sponsor: VeroScience

OSE RCM #: 2008-811

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.***

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EXECUTIVE SUMMARY

The proposed name, Cycloset, has some similarity to other proprietary drug names, but the findings of the Failure Mode and Effects Analysis (FMEA) indicates that the proposed name is not vulnerable to name confusion that could lead to medication errors. Thus, the Division of Medication Error Prevention and Analysis does not object to the use of the proprietary name, Cycloset, for this product.

If any of the proposed product characteristics as stated in this review are altered prior to approval of the product, we rescind this Risk Assessment finding, and recommend that the name be resubmitted for review.

Furthermore, this name must be re-evaluated upon submission of the NDA and approximately 90 days prior to the expected action date of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Metabolism and Endocrinology Products for assessment of the proprietary name, Cycloset, regarding potential name confusion with other proprietary or established drug names. The proposed product design, container label, and insert labeling were provided by the sponsor, and evaluated for their potential to contribute to medication errors.

1.2 PRODUCT INFORMATION

Cycloset (bromocriptine mesylate quick release) is a pending NDA with an anticipated action date of October 15, 2008. This application is a re-submission in response to an approvable letter issued by the Agency on October 15, 1999. Cycloset is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. It is available in one strength, 0.8 mg tablets, and the recommended dose of Cycloset is 1.6 mg to 4.8 mg (two to six tablets) to be taken once daily within two hours of waking.

Bromocriptine mesylate is also marketed under the proprietary name Parlodel® as an oral tablet available in 2.5 mg and 5 mg. Generic equivalent products also exist but do not have a proprietary name.

2 METHODS AND MATERIALS

This section consists of methods and materials used by medication error staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment). The primary focus for this assessment is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.¹

2.1 PROPRIETARY NAME RISK ASSESSMENT

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name, Cycloset, and the proprietary and established names of drug products

existing in the marketplace and those pending IND, NDA, and ANDA products currently under review by the Agency.

For the proprietary name, Cycloset, the medication error staff of the Division of Medication Error Prevention and Analysis search a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Sections 2.1.1 for detail) and held an CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see 2.1.1.2). The Division also conducts internal CDER prescription analysis studies (see 2.1.2), and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment (see detail 2.1.4).

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see detail 2.1.4). The overall risk assessment is based on the findings of a Failure Modes and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.¹ FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. The Division of Medication Error Prevention and Analysis uses the clinical expertise of the medication error staff to anticipate the conditions of the clinical setting that the product is likely to be used in based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap, or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. As such, the Staff considers the product characteristics associated with the proposed drug throughout the risk assessment, since the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the proposed product, the proposed indication, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, the Division of Medication Error Prevention and Analysis considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.²

2.1.1 Search Criteria

The Medication Error Staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted as outlined in Appendix A.

For this review, particular consideration was given to drug names beginning with the letter 'C' when searching to identify potentially similar drug names, as 75% of the confused drug names

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

² Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.³⁴

To identify drug names that may look similar to Cycloset, the Staff also consider the other orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (eight letters), upstrokes (three, capital letter 'C', lower case 'l' and 't'), downstrokes (lowercase 'y'), cross-strokes (lower case 't'), and dotted letters (none). Additionally, several letters in Cycloset may be vulnerable to ambiguity when scripted, including the letter 'C' may appear as 'A', 'O', 'F' or 'G'; lower case 'o' may appear as a lower case 'e' or 'a' and lower case 't' may appear as 'b'. As such, the Staff also considers these alternate appearances when identifying drug names that may look similar to Cycloset.

When searching to identify potential names that may sound similar to Cycloset, the Medication Error Staff search for names with similar number of syllables (three), stresses (Cy-CLO-set or Cyclo-SET), and placement of vowel and consonant sounds. The medication error staff also considers other variations where the 'Cy' sound may be interpreted as 'Si'. The sponsor's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

The Staff also consider the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting. For this review, the Medication Error Staff were provided with the following information about the proposed product: the proposed proprietary name (Cycloset), the established name (bromocriptine mesylate quick release), proposed indication (as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes), strength (0.8 mg), dose (2-6 tablets), frequency of administration (daily within two hours of waking), route (oral) and dosage form of the product (tablet). Appendix A provides a more detailed listing of the product characteristics the Medication Error Staff generally take into consideration.

Lastly, the Medication Error Staff also consider the potential for the proposed name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. As such, these broader safety implications of the name are considered and evaluated throughout this assessment and the Medication Error Staff provide additional comments related to the safety of the proposed name or product based on their professional experience with medication errors.

2.1.1.1 Database and Information Sources

The proposed proprietary name, Cycloset, was provided to the medication error staff of the Division of Medication Error Prevention and Analysis to conduct a search of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to Cycloset using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 7. To complement the process, the Medication Error Staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and

³ Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at <http://www.ismp.org/Tools/confuseddrugnames.pdf>

⁴ Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the Medication Error Staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

2.1.1.2 CDER Expert Panel Discussion

An Expert Panel Discussion is held by the Division of Medication Error Prevention and Analysis to gather CDER professional opinions on the safety of the product and the proprietary name, Cycloset. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of the Division of Medication Error Prevention and Analysis Medication Errors Prevention Staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC).

The pooled results of the medication error staff were presented to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

2.1.2 FDA Prescription Analysis Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Cycloset 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. The studies employ a total of 123 healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The results are used by the Safety Evaluator to identify any orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of Cycloset in handwriting and verbal communication of the name, inpatient medication orders and outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These prescriptions are optically scanned and one prescription is delivered to a random sample of 123 participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are 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 send their interpretations of the orders via e-mail to the medication error staff.

Figure 1. 0609 Study (conducted on June 9, 2008)

HANDWRITTEN PRESCRIPTION AND MEDICATION ORDER	VERBAL PRESCRIPTION
<p><u>Inpatient Medication Order:</u></p> <p><i>2 Cycloset 0.8 mg 2 tablets by mouth once daily</i></p>	<p>Cycloset 0.8 mg #120</p>
<p><u>Outpatient Prescription Order:</u></p> <p><i>Cycloset 0.8mg #120 TT takes po once daily</i></p>	<p>Take 2 tablets po once daily</p>

2.1.3 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1.1, the Safety Evaluator Risk Assessment applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Modes and Effects Analysis and provide an overall risk of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.⁵ When applying FMEA to assess the risk of a proposed proprietary name, the Division of Medication Error Prevention and Analysis seeks to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to look- or sound-alike drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is not yet marketed, the Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Appendix A. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, expert panel evaluation, and studies, and identifies potential failure modes by asking: "Is the name Cycloset convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?" An affirmative answer indicates a failure mode and represents a potential for Cycloset to be confused with another proprietary or established drug name because of look- or

⁵ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names possess similarity that would cause confusion at any point in the medication use system and the name is eliminated from further review.

In the second stage of the Risk Assessment, all potential failure modes are evaluated to determine the likely *effect* of the drug name confusion, by asking "Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?" The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would ultimately not be a source of medication errors in the usual practice setting, the name is eliminated from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend that an alternate proprietary name be used. In rare instances, the FMEA findings may provide other risk-reduction strategies, such as product reformulation to avoid an overlap in strength or an alternate modifier designation may be recommended as a means of reducing the risk of medication errors resulting from drug name confusion.

The Division of Medication Error Prevention and Analysis will object to the use of proposed proprietary name when the one or more of the following conditions are identified in the Safety Evaluator's Risk Assessment:

1. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].
2. The Division of Medication Error Prevention and Analysis identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
4. The proposed proprietary name contains an USAN stem, particularly in a manner that is contradictory to the USAN Council's definition.
5. Medication Error Staff identify a potential source of medication error within the proposed proprietary name. The proprietary name may be misleading, or inadvertently introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug name and another drug product.

In the event that the Division of Medication Error Prevention and Analysis objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, the Division will provide a contingency objection based on the date of approval: whichever product is awarded approval first has the right to the use the name, while the Division will recommend that the second product to reach approval seek an alternative name.

If none of these conditions are met, then the Division of Medication Error Prevention and Analysis will not object to the use of the proprietary name. If any of these conditions are met, then the Division will object to the use of the proprietary name. The threshold set for objection to the proposed proprietary name may seem low to the Sponsor; however, the safety concerns set forth in

criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the IOM, WHO, JCAHO, and ISMP, have examined medication errors resulting from look- or sound-alike drug names and called for Regulatory Authorities to address the issue prior to approval.

Furthermore, the Division of Medication Error Prevention and Analysis contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, can be identified and remedied prior to approval to avoid patient harm.

Additionally, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational efforts and so on are low-leverage strategies that have proven to have limited effectiveness at alleviating the medication errors involving drug name confusion. Higher-leverage strategies, such as drug name changes, have been undertaken in the past; but at great financial cost to the Sponsor, and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for the approving the error-prone proprietary name. Moreover, even after Sponsor's have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioner's vocabulary, and as such, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, the Division of Medication Error Prevention and Analysis believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval (see limitations of the process).

If the Division of Medication Error Prevention and Analysis objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the FMEA process is used to identify strategies to reduce the risk of medication errors. The Division of Medication Error Prevention and Analysis is likely to recommend that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for the Division of Medication Error Prevention and Analysis to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name, and so the Division of Medication Error Prevention and Analysis may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

2.2 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.⁶

⁶ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

Because DMETS staff analyze reported misuse of drugs, DMETS staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. DMETS uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Sponsor submitted the following labels and insert labeling for our review (see Appendix I and J for images):

- Retail Container Label (200 and 600 tablets)
- Physician Samples Container Label (21 tablets)
- Package Insert (images not included)

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

Our search of the internet, several standard published databases and information sources (see Section 7 References) identified 23 names as having some similarity to the name Cycloset: Glyset, Ciclesonide, Cyclocort, Cyclogyl, Cyclovar, Cylert, Aplisol, Cyclopar, Adacel, Adalat, Casodex, Cyclosporine, Cyclease-1, Cyclotab, Cyclessa, Cytotec, Cycloserine, Cyclinex-1, Cytomel, Citrucel, Cylcomen, Cytoxin, and Colchicine.

Fifteen of the 23 names were thought to look like Cycloset (Glyset, Ciclesonide, Cyclocort, Cyclogyl, Cyclovar, Cylert, Aplisol, Cyclopar, Adacel, Adalat, Casodex, Cyclosporine, Cyclease-1, Cyclotab and colchicine) and 5 names (Cyclessa, Cytotec, Cycloserine, Cyclinex-1 and Cytomel) were thought to look and sound similar to Cycloset. Three names (Citrucel, Cylcomen and Cytoxin) were thought to sound like Cycloset.

No USAN stems were identified in Cycloset as of July 8, 2008.

3.1.2 CDER Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by the Division of Medication Error Prevention and Analysis staff (see section 3.1.1. above), but did not identify any additional names with similarity to Cycloset.

In addition, the Expert Panel raised a concern about potential medication error issues regarding this product. Specifically, the product name, Cycloset, creates a dual trade name for the established name, bromocriptine mesylate, which is currently marketed as a generic product and also under the trade name Parlodel.

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name.

3.1.3 FDA Prescription Analysis Studies

A total of 28 practitioners responded, but none of the responses overlapped with any existing or proposed drug names. About 82% of the participants (n=23) interpreted the name correctly as "Cycloset," with correct interpretation occurring more frequently in the written studies. The remainder of the responses misinterpreted the drug name. The majority of misinterpretations occurred in the phonetic prescription study, 3 respondents misinterpreted 'Cycloset' as 'Fisofette',

		Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	<ul style="list-style-type: none"> • Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B:

CDER Prescription Study Responses- Cycloset Study 0609

Study Response	Study Response	Study Response
Cycloset	Cycloset	Cycloset
Cycloset	Cycloset	Cycloset
Cycloset	Cycloset	Fisofette
Cycloset	Cycloset	Cyplist
Cycloset	Cycloset	Cyclofet
Cycloset	Cycloset	
Cyclopet	Cycloset	
Cycloset	Cycloset	
Cycloset	Cycloset	
	Cycloset	

'Cycliset or 'Cyclofet'. In the written prescription studies, the letter 's' was misinterpreted as 'p' by one respondent and the letter 'r' was inserted before the final 't'. See Appendix A for the complete listing of interpretations from the verbal and written prescription studies.

3.1.4 Safety Evaluator Risk Assessment

Independent searches by the primary Safety Evaluator identified two additional names thought to look similar to Cycloset[†] _____ and Cyclaine). As such, a total of 24 names (22 identified by the CDER Expert panel discussion and 2 from the primary safety evaluator) were analyzed to determine if the drug names could be confused with Cycloset and if the drug name confusion would likely result in a medication error.

b(4)

All of the identified names were determined to have some orthographic and/or phonetic similarity to Cycloset, and thus determined to present some risk for confusion. Failure mode and effects analysis (FMEA) was then applied to determine if the proposed name, Cycloset, could potentially be confused with any of the 24 names and lead to medication error.

This analysis determined that the name similarity between Cycloset and the identified names was unlikely to result in medication errors for all 24 product names for the reasons described in Appendices C-H.

3.2 LABEL AND LABELING RISK ASSESSMENT

Review of the container labels, carton labeling and package insert identified several potential sources of medication error.

3.2.1 General Comment

The dosage form, described as quick release or QR, is not defined by USP or the CDER Data Standards Manual.

3.2.2 Retail and Physician Container Labels

The company name and logo is larger than the proprietary name. Additionally, it is located above the proprietary name.

The established name is less than ½ the size of the proprietary name.

The net quantity statement is located directly below the dosage strength.

3.2.3 Package Insert

Patients are instructed to take their morning dose of Cycloset between 8 am and 10 am under the Patient Counseling Information sections of labeling (sections 17.1 and 17.3).

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

The results of the Proprietary Name Risk Assessment found that the proposed name, Cycloset, has some similarity to other proprietary drug names, but the findings of the FMEA indicates that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors.

The findings of the Proprietary Name Risk Assessment are based upon current understanding of factors that contribute to medication errors involving name confusion. Although we believe the

findings of the Risk Assessment to be robust, our findings do have limitations. First, because our assessment involves a limited number of practitioners, it is possible that the analysis did not identify a potentially confusing name. Also, there is some possibility that our Risk Assessment failed to consider a circumstance in which confusion could arise. However, the Division of Medication Error Prevention and Analysis believes that these limitations are sufficiently minimized by the use of an Expert Panel, the CDER Prescription Studies that involved 123 CDER practitioners, and, in this case, the data submitted by the Sponsor from an independent proprietary name risk assessment firm, which included the responses of frontline practitioners.

However, our risk assessment also faces limitations beyond the control of the Agency. First, our risk assessment is based on current health care practices and drug product characteristics, future changes to either could increase the vulnerability of the proposed name to confusion. Since these changes cannot be predicted for or accounted by the current Proprietary Name Risk Assessment process, such changes limit our findings. To help counterbalance this impact, the Division of Medication Error Prevention and Analysis recommends that the proprietary name be re-submitted for review when the NDA is filed and 90 days prior to the goal date.

4.2 LABEL AND LABELING RISK ASSESSMENT

The results of the Label and Labeling Risk Assessment found that the presentation of information and design of the proposed carton and container labels appears to be vulnerable to confusion that could lead to medication errors.

4.2.1 General Comment

The dosage form, described as quick release or QR, is not defined by USP or the CDER Data Standards Manual and therefore should be removed from all labels and from all sections of the package insert.

4.2.2 Retail and Physician Container Labels

The prominence and size of the proprietary name in comparison to the company name and logo is inadequate. Additionally, the location of the company logo (above Cycloset) is not appropriate since it is located in close proximity to the proprietary name. These attributes make the logo more prominent than other critical information. The size of the company name and logo should be decreased so as not to interfere with the readability of the proprietary name and strength.

In accordance with 21 CFR 201.10(g)(2), the established name on all container labels must be at least $\frac{1}{2}$ the size of the proprietary name.

The net quantity statement which is located directly below the dosage strength is intervening with the readability of the strength and should be relocated away from the dosage strength (i.e. upper or bottom corner of the principle display panel).

4.2.3 Package Insert

In the Patient Counseling Sections of labeling (sections 17.1 and 17.3) patients are instructed to take their morning dose of Cycloset between 8 am and 10 am. Depending on each individual patients sleeping patterns, listing a specific time of day for dose administration could create confusion for the patient and lead to possible missed doses. It is recommended that the specific time to administer the dose be omitted (unless there is a compelling reason to do so) and that these sections of labeling be revised to be consistent with the Dosage and Administration section of labeling which states to take the recommended dose of Cycloset within 2 hours after waking in the morning.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Cycloset, does not appear to be vulnerable to name confusion that could lead to medication errors. As such, the Division of Medication Error Prevention and Analysis does not object to the use of the proprietary name, Cycloset, for this product. *

5.1 COMMENTS TO THE DIVISION

The Division of Medication Errors 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 us on any communication to the sponsor with regard to this review. If you have further questions or need clarifications, please contact Cheryl Campbell, project manager, at 301-796-0723.

1. The Division of Medication Error Prevention and Analysis has no objection to the use of the proprietary name Cycloset for this product. If any of the proposed product characteristics as stated in this review are altered prior to approval of the product, we rescind this Risk Assessment finding, and recommend that the name be resubmitted for review. If the product approval is delayed beyond 90 day from the date of this review, the proposed name must be resubmitted for evaluation.
2. The Division of Medication Error Prevention recommends that the Division consult Richard Lostritto, Chair of the CDER Labeling and Nomenclature Committee (LNC), and the assigned ONDQA Chemist regarding the proper designation of the established name.

5.2 COMMENTS TO THE APPLICANT

5.2.1.1 Proprietary Name

The Division of Medication Error Prevention and Analysis has no objections to the use of the proprietary name Cycloset for this product.

5.2.1.2 Retail and Physician Container Labels

1. The size of the company name and logo should be decreased so as not to interfere with the readability of the proprietary name and strength.
2. In accordance with 21 CFR 201.10(g)(2), the prominence of the established name should be increased to at least ½ the size of the proprietary name, and 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. We note that in some of the labels the established name appears to be of adequate size but in other labels it does not. Since the proprietary name for this product is bolded in the labels the size of the established name may need to be increased more than ½ the size of the proprietary name to satisfy this requirement
3. Relocate the net quantity statement to an area on the label that doesn't intervene with the dosage strength statement (i.e. upper or bottom corner of the principle display panel).

5.2.1.3 Package Insert

In the Patient Counseling Sections of labeling (sections 2.1, 17.1 and 17.3) patients are instructed to take their morning dose of Cycloset between 8 am and 10 am. Depending on each individual patients sleeping patterns, listing specific times for dose administration could create confusion for the patient and lead to possible missed doses. The specific time to administer the dose should be omitted (unless there is a compelling reason not to) and that these sections of labeling be revised to be consistent with the Dosage and Administration section of labeling which states to take the recommended dose of Cycloset within 2 hours after waking in the morning.

6 REFERENCES

1. ***Micromedex Integrated Index*** (<http://csi.micromedex.com>)

Contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. ***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. Likewise, an orthographic algorithm exists which operates in a similar fashion. This is a database which was created for the Division of Medication Error Prevention and Analysis, FDA.

3. ***Drug Facts and Comparisons, online version, St. Louis, MO***
(<http://factsandcomparisons.com>)

Drug Facts and Comparisons is a compendium organized by therapeutic course; contains monographs on prescription and OTC drugs, with charts comparing similar products.

4. ***AMF Decision Support System [DSS]***

DSS is a government database used to track individual submissions and assignments in review divisions.

5. ***Division of Medication Errors Prevention and Analysis proprietary name consultation requests***

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

6. ***Drugs@FDA*** (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and "Chemical Type 6" approvals.

7. ***Electronic online version of the FDA Orange Book***
(<http://www.fda.gov/cder/ob/default.htm>)

Provides a compilation of approved drug products with therapeutic equivalence evaluations.

8. U.S. Patent and Trademark Office (<http://www.uspto.gov>)

Provides information regarding patent and trademarks.

9. Clinical Pharmacology Online (www.clinicalpharmacology-ip.com)

Contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. Provides a keyword search engine.

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

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

11. Natural Medicines Comprehensive Databases (www.naturaldatabase.com)

Contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

12. Stat!Ref (www.statref.com)

Contains full-text information from approximately 30 texts. Includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology and Dictionary of Medical Acronyms Abbreviations.

13. USAN Stems (<http://www.ama-assn.org/ama/pub/category/4782.html>)

List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

Contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

15. Lexi-Comp (www.lexi.com)

A web-based searchable version of the Drug Information Handbook.

16. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

The medication error staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. The Division of Medication Error Prevention and Analysis also compare the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. The Medication Error Staff also examine the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly *and* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has led to medication errors. The medication error staff apply their expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (i.e. "T" may look like "F," lower case 'a' looks like a lower case 'u,' etc), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see detail in Table 1 below). Additionally, since verbal communication of medication names is common in clinical settings, the Medication Error Staff compare the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, the Division of Medication Error Prevention and Analysis will consider the Sponsor's intended pronunciation of the proprietary name. However, because the Sponsor has little control over how the name will be spoken in practice, the Division of Medication Error Prevention and Analysis also considers a variety of pronunciations that could occur in the English language.

Table 1. Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name

Type of similarity	Considerations when searching the databases		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	<ul style="list-style-type: none"> Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstrokes Downstrokes	<ul style="list-style-type: none"> Names may look similar when scripted, and lead to drug name confusion in written communication

Appendix C: Names lacking convincing orthographic and/or phonetic similarities with Cycloset

Proprietary Name	Similarity to Cycloset
Ciclesonide	Look Alike
Adacel	Look Alike
Adalat	Look Alike
Cyclosporin	Look Alike
Cycloserine	Look and Sound Alike

Appendix D: Names of products withdrawn from the market

Proprietary Name	Reason	Date
Cyclocort (amcinonide) Cream, Lotion and Gel	NDA Withdrawn (available in all formulations under the established name only)	September 28, 2006
Cyclaine (hexylcaine hydrochloride)	Withdrawn by Commissioner (no generics available)	August 7, 1997
Cyclopar (tetracycline) Capsules	NDA Withdrawn (available in generic and other brand name formulations)	June 30, 1992
Cyclotab	Withdrawn by applicant (FDA issued an NA action on 7/29/1980)	July 12, 1992

Appendix E: Unapproved Proposed Proprietary name

Proprietary Name	Status
_____ (not reviewed by DMEPD)	Unapproved product; FDA issued an NA action on June 1, 1978

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Appendix F: Names of Discontinued Products

Proprietary Name	Status
Cylert (pimoline) Tablets	Product Discontinued for safety reasons with no plans for remarketing; no generics available

Appendix G: Products with no overlap in strength and usual dosage

Product Name with Strength and Usual Dosage	Similarity to Proprietary Name	Strength	Usual Dose (if applicable)
Cycloset (bromocriptine mesylate)		0.8 mg	1.6 mg to 4.8 mg (2 to 6 tablets) once daily in AM
Glyset (miglitol)	Look Alike	25 mg, 50 mg and 100 mg Tablets	Individualized for patient to a maximum dose of 1000 mg daily
Cyclogyl (cyclopentolate)	Look alike	0.5 %, 1 % and 2 % Ophthalmic Drops	To be used 40-50 minutes prior to procedure
Cyclella (desogestrel, ethinyl estradiol)	Look and sound alike	0.1 mg/ 0.025 mg, 0.125 mg/0.025 mg and 0.15 mg and 0.025 mg Tablets	One tablet daily

Cytotec (misoprostol)	Look and sound alike	0.1 mg and 0.2 mg Tablets	One to two tablets four times daily
Cytomel (liothyronine)	Look and sound alike	5 mcg, 25 mcg and 50 mcg Tablets	Take 25 mcg- 105 mcg daily
Cytoxan (cyclophosphamide)	Sound Alike	25 mg and 50 mg tablets 100 mg, 200 mg, 500 mg, 1 Gm and 2 Gm Injectable	40 mg to 50 mg/kg/day in divided doses for 2-5 days 1 mg to 5 mg/kg/day as a maintenance dose (tablet formulation)
Citricel (methylcellulose)	Sound Alike	2 Gm per teaspoon 500 mg tablet	2 GM given 1-3 times daily
Cyclomen (danazol)	Sound Alike	50 mg, 100 mg and 200 mg capsules	100 mg to 400 mg daily in divided doses
Colchicine Tablets 0.5 mg granules and 0.6 mg tablets	Look Alike	0.5 mg granules 0.6 mg tablets	0.5 mg or 0.6 mg hourly at onset of attack until pain relief or diarrhea occurs, 0.5 mg or 0.6 mg can be given every 2-3 hours after initial attack Maintenance- 0.5 mg or 0.6 mg three to four times weekly up to 2-3 times daily

Appendix H: Potential confusing name with overlap in single strength availability

Cycloset (bromocriptine mesylate)	0.8 mg tablets	1.6 mg to 4.8 mg once daily in AM
Failure Mode: Name confusion	Causes (could be multiple)	Effects
Cyclovar (L-Argine) 250 mg tablets (located on the natural medicines website, however, unable to locate at any other drug store/vitamin distribution sites)	Orthographic similarity (names both have 'Cyclo' in the same position; names are same in length) Both products available in single strength only	Orthographic differences in the suffix of the name along with differences in the products characteristics minimize the likelihood of medication error in the usual practice setting. Rationale: Cyclovar is an amino acid supplement available as an OTC. To further distinguish the products, Cycloset dosages will likely be written on prescriptions since doses (e.g 1.6 mg to 4.8 mg [2 to 6 tablets]) of this product are individualized for each patient. Orthographic differences are introduced by 'set' and 'var'.

<p>Aplisol (tuberculin purified protein) 5 tu/0.1 mL</p>	<p>Orthographic similarity (names both have similar shape and are similar in length)</p> <p>Both products available in single strength only</p>	<p>Significant differences in product characteristics for these products.</p> <p>Rationale: There are significant differences in product characteristics since Aplisol is for subcutaneous PPD placement and will be administered by a health care practitioner and not the patient.</p>
<p>Casodex (bicalutamide) 50 mg</p>	<p>Orthographic similarity (names both have 'C' in the same position and overlap in the letter 'o' and 'e' and are similar in length)</p> <p>Both products available in single strength only</p>	<p>Orthographic differences in the name along with differences in the products characteristics minimize the likelihood of medication error in the usual practice setting.</p> <p>Rationale: Casodex is given in conjunction with a LHRH analogue an amino acid nutritional supplement available as an OTC. To further distinguish the products, Cycloset dosages will likely be written on prescriptions since doses (e.g 1.6 mg to 4.8 mg [2 to 6 tablets]) of this product are individualized for each patient. Orthographic differences are introduced by the additional downstroke (y) and cross-stroke (T) in cycloset.</p>
<p>Cyclease-1 (desogestrel, ethinyl estradiol)</p>	<p>Orthographic similarity (names both have 'Cycl' in the same position and are similar in length)</p> <p>Both products available in single strength only</p>	<p>Differences in the products characteristics minimize the likelihood of medication error in the usual practice setting.</p> <p>Rationale: Cyclease-1 is available in a unit dose pack indicated for pregnancy prevention. Additionally, Cycloset dosages will likely be written on prescriptions since doses (e.g 1.6 mg to 4.8 mg [2 to 6 tablets]) of this product are individualized for each patient.</p>
<p>Cyclinex-1 (amino acid powder)</p>	<p>Orthographic similarity (names both have 'Cycl' in the same position and are similar in length)</p> <p>Both products available in single strength only</p>	<p>Differences in the products characteristics minimize the likelihood of medication error in the usual practice setting.</p> <p>Rationale: Cyclinex-1 is a nutritional therapy powder and Cycloset is a tablet. To further distinguish the products, Cycloset dosages will likely be written on prescriptions since doses (e.g 1.6 mg to 4.8 mg [2 to 6 tablets]) of this product are individualized for each patient.</p>

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