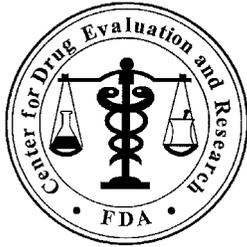


**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22483Orig1s000**

**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: June 12, 2009

To: Susan J. Walker, MD  
Director, Division of Dermatological and Dental Products

Through: Kellie Taylor, PharmD, Team Leader  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: Cathy A. Miller, BSN, MPH, Safety Evaluator  
Division of Medication Error Prevention and Analysis  
Patty Greene, Pharm.D., Drug Utilization Analyst  
Division of Epidemiology

Subject: Proprietary Name Review

Drug Name(s): Zyclara (Imiquimod) Cream  
3.75%

Application Type/Number: NDA 22-483

Applicant/Applicant: Graceway Pharmaceuticals, LLC

OSE RCM #: 2009-487

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

# CONTENTS

EXECUTIVE SUMMARY .....	3
1 BACKGROUND .....	3
1.1 Introduction .....	3
1.2 Product Information .....	3
1.3 Regulatory History .....	4
2 METHODS AND MATERIALS .....	4
2.1 Proprietary Name Risk Assessment .....	4
3 RESULTS.....	13
3.1 Proprietary Name Risk Assessment .....	13
4 DISCUSSION .....	17
4.1 Imiquimod Dosing Regimen .....	17
4.2 Risk of Concomitant Therapy .....	18
4.3 Varying Treatment Regimens .....	19
4.4 Past Agency Precedence for Dual Tradename Decisions .....	20
4.5 Potential for Product Extension and Future Availability of Generics.....	20
5 CONCLUSIONS AND RECOMMENDATIONS .....	21
5.1 Comments To The Applicant.....	21
6 REFERENCES .....	22
Databases.....	22
APPENDICES .....	26

## **EXECUTIVE SUMMARY**

Zyclara is the proposed name for Imiquimod 3.75 % Cream. The Applicant currently markets this product under the name, Aldara. Aldara is indicated for the treatment of actinic keratosis, superficial basal cell carcinoma and external genital warts whereas; Zyclara will be indicated only for the treatment of actinic keratosis. The Applicant presented a justification for the use of a new proprietary name that includes “having separate labeling and a separate brand name is in the best interest of the patient as it ensures that the drug will be used correctly and will avoid confusion that could cause medical errors for the new and original product”. However, the Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Dermatological and Dental Products (DDDP) find that the Applicant’s proposal to use two different names (Zyclara and Aldara) for Imiquimod cream presents a safety risk associated with potential concomitant treatment which could occur in patients being treated for more than one indication (actinic keratosis, superficial basal cell carcinoma and/or genital warts) by different prescribing providers, resulting in the potential for overdose that could cause increased systemic exposure to the active ingredient, Imiquimod. Additionally, Aldara and Zyclara have an overlapping indication of use, actinic keratosis. It is possible that a patient may be treated for the same indication of use by different prescribers. The use of the same active ingredient may go undetected because the dosing regimen for this indication of use is different between products. Aldara recommends a twice weekly application whereas Zyclara recommends a daily application at bedtime. In either case, concomitant treatment may also increase the potential for adverse reactions and local skin reactions seen with the use of Imiquimod.

We further find that the safety risk associated with the inadvertent concomitant use of both strengths of the product at the same time is more likely to occur if the product has two different proprietary names. This safety risk can best be averted if both strengths are managed under the same proprietary name with one combined package insert. Thus, DMEPA objects to the use of the name, Zyclara for the new 3.75 % Imiquimod cream and recommends that both the 3.75 % and 5 % strengths be managed under the same tradename, Aldara, and one combined package insert labeling for both strengths.

## **1 BACKGROUND**

### **1.1 INTRODUCTION**

This review was written in response to Graceway Pharmaceuticals, LLC on March 13, 2009, for the proprietary name review of proposed name, Zyclara, for potential name confusion with other proprietary or established drug names in the usual practice setting. The Applicant also submitted draft container labels and carton labeling, which will be reviewed in a separate DMEPA review.

### **1.2 PRODUCT INFORMATION**

The Applicant currently markets Imiquimod 5 % with the proprietary name, Aldara. Aldara is indicated for the treatment of actinic keratosis, superficial basal cell carcinoma and external genital warts. Zyclara (Imiquimod) 3.75 % Cream, is indicated for the

topical treatment of clinically typical visible or palpable actinic keratoses of the face or balding scalp in immunocompetent adults. Zyclara is applied daily to the skin of the affected area (either the face or balding scalp) at bedtime for two 2-week treatment cycles separated by a 2-week no-treatment period. It is recommended that the treatment area be washed with mild soap and water eight hours following application.

Zyclara is supplied in single-use packets, each containing 250 mg of cream, equivalent to 9.4 mg of Imiquimod. Up to two packets may be applied topically to treatment area.

### **1.3 REGULATORY HISTORY**

Imiquimod cream 5% was approved February 27, 1997, (NDA 20-723) under the tradename, Aldara, for the indication of genital and perianal warts. On May 1, 2003, the Applicant submitted an efficacy supplement for the new indication of actinic keratosis to the new drug application which was approved on March 2, 2004, and on June 9, 2003, the Applicant submitted an efficacy supplement for the indication of superficial basal cell carcinoma (sBCC) which was approved on July 14, 2004.

On December 19, 2008, the Applicant submitted new drug application (NDA 22-483) for a new 3.75 % strength of Imiquimod cream, for the indication of actinic keratosis, proposing a new tradename, Zyclara, for this product. The 3.75 % Imiquimod cream provides a different dosage regimen (shorter duration and daily application) over a larger surface area (entire face or balding scalp versus 25 cm<sup>2</sup> with the use of the 5 % strength) along with same mechanism of action as the original Aldara 5 % strength cream. The Applicant cites concern about the possibility of medication errors in patients who may be prescribed either the proposed Zyclara 3.75 % cream or the Aldara 5 % cream, for the treatment of actinic keratosis. They state that the use of either product according to the other product's dosing instructions could impact patient safety or product effectiveness. In order to minimize the potential for medication errors, they propose the new tradename, Zyclara, along with a separate package insert specifically designed to describe only the clinical trials data and dosing instructions for the 3.75 % Imiquimod cream product.

## **2 METHODS AND MATERIALS**

This section describes the methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) when conducting a proprietary name risk assessment (See 2.1 Proprietary Name Risk Assessment). The primary objective for the assessment is to identify and remedy potential sources of medication error prior to drug approval. DMEPA 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.<sup>1</sup>

### **2.1 PROPRIETARY NAME RISK ASSESSMENT**

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

---

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

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

For the proposed proprietary name, DMEPA staff searched a standard set of databases and information sources to identify names with orthographic and phonetic similarity (See 2.1.1 for details) and held a Center for Drug Evaluation and Research (CDER) Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (See 2.1.1.2). DMEPA staff also conducts internal CDER prescription analysis studies. When provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment.

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 2.1.4 for details). 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.<sup>2</sup> Additionally, for this review, DMEPA conducted an additional evaluation to determine whether marketing a dual tradename (Zyclara and Aldara) would be less prone to medication errors than having one tradename for both Imiquimod cream strengths (3.75 % and 5 %). FMEA is used to analyze whether the drug names identified with orthographic or phonetic similarity to the proposed proprietary name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used 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. Accordingly, the DMEPA staff considers the product characteristics associated with the proposed drug throughout the risk assessment because 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 proprietary name include, but are not limited to, established name of the proposed product, proposed indication of use, 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

---

<sup>2</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.<sup>3</sup>

### ***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 ‘Z’ 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.<sup>4,5</sup>

To identify drug names that may look similar to ‘Zyclara’, the DMEPA staff also considers the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (seven letters), and upstrokes (two, one capital letters ‘Z’ and the lower case ‘l’). Additionally, several letters in Zyclara may be vulnerable to ambiguity when scripted (see Appendix B). As a result, the DMEPA staff also considers these alternate appearances when identifying drug names that may look similar to Zyclara.

When searching to identify potential names that may sound similar to Zyclara, the DMEPA staff searches for names with similar number of syllables (three), stresses (ZY-cla-ra, zy-CLA-ra or zy-cla-RA), and placement of vowel and consonant sounds. Additionally, the DMEPA staff considers that pronunciation of parts of the name can vary (See Appendix B). The Applicant’s intended pronunciation of Zyclara is zī-clar-a. Names are often mispronounced and/or spoken with regional accents and dialects, so other potential pronunciations of the name are considered.

The DMEPA staff also considers the product characteristics associated with the proposed drug throughout the identification of similar drug names because the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting. For this review, the following information was provided about the proposed product to the medication error staff: proposed proprietary name (Zyclara), proposed established name (Imiquimod), proposed indication of use (topical treatment of clinically typical visible or palpable actinic keratoses of the face or balding scalp in immunocompetent adults), strength (3.75 %), dose (apply one to two packets to affected area), frequency of administration (once daily), duration of use (two 2-week treatment cycles separated by a 2-week no-treatment period), route of administration (topical), and dosage form (cream).

---

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

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

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

Lastly, the DMEPA staff also considers the potential for the proposed proprietary 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. Consequently, these broader safety implications of the name are considered and evaluated throughout this assessment and the medication error staff provides additional comments related to the safety of the proposed proprietary name or product based on professional experience with medication errors.

#### **2.1.1.1 Database and Information Sources**

The proposed proprietary name 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 the proposed proprietary name using the criteria outlined in Section 2.1.1. A standard description of the databases used in the searches is provided in Section 7. To complement the process, DMEPA used 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 reviewed the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators were then pooled and presented to the CDER 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 proposed product and the proposed proprietary name. The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC). Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed.

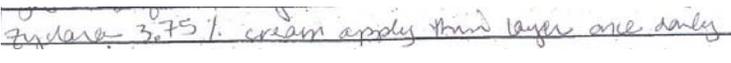
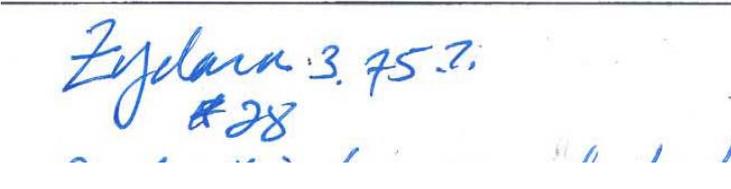
The pooled results of the DMEPA staff were presented to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the Safety Evaluator to supplement the pooled results, or general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

**2.1.2 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 the proposed proprietary name 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 (one hundred twenty-three) 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 the proposed proprietary name 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 orders are optically scanned and one prescription is delivered to a random sample of the 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 DMEPA.

**Figure 1. Zyclara Rx Study (conducted on April 28, 2009)**

HANDWRITTEN REQUISITION MEDICATION ORDER	VERBAL PRESCRIPTION
<p><u>Inpatient Medication Order:</u></p> 	<p>Zyclara 3.75 % #28 Apply thin layer to skin of affected area daily as directed.</p>
<p><u>Outpatient Prescription:</u></p> 	

**2.1.3 Comments from the OND Review Division**

DMEPA requests the regulatory division in the Office of New Drugs responsible for the application for their comments or concerns with the proposed proprietary name and any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with DDMAC’s decision on the name. Any comments or concerns are addressed in the safety evaluator’s assessment. For this review, DMEPA

also sought a preliminary meeting with the Division of Dermatological and Dental Products to discuss the product history and review potential concerns with the proposal for a new tradename for the 3.75 % Imiquimod product.

The regulatory division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The regulatory division is requested to concur/not concur with DMEPA's final decision.

#### ***2.1.4 Aldara Drug Utilization Data Sources and Methods***

As part of our Proprietary Name evaluation for the proposed name, Zyclara, DMEPA sought an analysis from the Division of Epidemiology. DMEPA requested information about current drug utilization for the marketed Imiquimod 5 % cream, marketed under the proprietary name, Aldara. We requested information about current drug usage, by prescriber type and diagnosis associated with use of Imiquimod, in order to assess the diversity of practitioner types who prescribe Aldara and the most common indications of use for which the product is prescribed.

IMS Health, IMS National Sales Perspectives™ data were used to determine the setting in which Aldara® (Imiquimod) cream was sold. Sales of this product by number of packs (boxes) sold from the manufacturer into the various retail and non-retail channels of distribution were analyzed for year 2008 (***data not provided***).<sup>6</sup> During the review period, retail settings (chain stores, independent pharmacies, and food stores) accounted for the majority of Aldara® (Imiquimod) cream sales [REDACTED] (b) (4) were sold to non-retail settings. Thus, the examination of Aldara (Imiquimod) cream utilization patterns focused on the outpatient setting, excluding mail order channels. The Division of Epidemiology staff examined the total dispensed prescriptions by prescribing specialties for Aldara® (Imiquimod) cream using SDI, Vector One®: National (VONA) (see Appendix 1 for full description) for calendar years 2004 through 2008. Indications associated with the use of Aldara® (Imiquimod) cream as reported by office-based physicians, were determined using SDI's Physician Drug and Diagnosis Audit (PDDA) for calendar years 2004 through 2008

#### ***2.1.5 Safety Evaluator Risk Assessment of the Proposed Proprietary Name***

Based on the criteria set forth in Section 2.1, the Safety Evaluator Risk Assessment applies his/her individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Mode and Effects Analysis and provides an overall risk assessment 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.<sup>7</sup> When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name as a result of the name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of

---

<sup>6</sup> IMS Health, IMS Nationals Sales Perspectives™, Data extracted 4-27-2009, Source file: 0904imi.q.DVR

<sup>7</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar 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 for this product. 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, Zyclara, 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 the Zyclara 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, then 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 not ultimately 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; for example, 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.

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

PROPRIETARY 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 (United States Adopted Names) 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. For example, 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 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, DMEPA 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 DMEPA will recommend that the second product to reach approval seek an alternative name.

If none of these criteria are met, then DMEPA will not object to the use of the proprietary name. If any of these criteria are met, then DMEPA will object to the use of the proposed 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 (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP), who 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 and other post-approval efforts are low-leverage strategies that have proven to have limited effectiveness at alleviating 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 practitioners' vocabulary, and as a result, 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 Section 4 for 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. In that instance, DMEPA may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

#### ***2.1.6 Adverse Events Reporting System (AERS) Database Search***

Since the Applicant markets the product under the name, Aldara, we searched the Adverse Events Reporting System (AERS) database using the search criteria from a pending post-marketing review currently underway for Aldara. For that review, the AERS search was conducted using the tradename "Aldara" and active ingredient "Imiquimod". The MedDRA High Level Group Term (HGLT) "Medication Errors" and Preferred Term (PT) "Pharmaceutical Product Complaint" were used to perform the search. DMEPA identified post-marketing errors with Aldara in response to reports of wrong frequency medication errors retrieved from this pending review (OSE Review #2006-785).

#### ***2.1.7 Applicant Justification for Labeling Separate from Aldara***

The Applicant submitted a document titled "Attachment 1: Justification for Labeling Separate from Aldara" with their request for review of proposed tradename 'Zyclara' on March 16, 2009. This document details product information about Imiquimod, including the regulatory history of Aldara 5 %, details about the investigational 3.75 % strength product, and comparisons between the 3.75 % and 5 % products. The report also includes an analysis to justify a separate tradename, 'Zyclara'. Their justification states that a separate tradename will avert product confusion, provide differentiation between the two strengths for adverse event reporting purposes, and a discussion surrounding Agency precedence for allowing separate labeling and separate brand names with other approved products. DMEPA considered the information as part of our analysis.

## **3 RESULTS**

### **3.1 PROPRIETARY NAME RISK ASSESSMENT**

#### ***3.1.1 Database and Information Sources***

The searches yielded a total of 17 names as having some similarity to the proposed name 'Zyclara'.

Fifteen of the names were thought to look like the proposed name 'Zyclara'. These include Byetta, Climara, Fludara, Lyclear, Lyrica, Lysodren, Zocor, Zycalcit, Zyclorax, Zyclorin, Zydalis, Zydone, Zyclus, Zymar, and Zyrtec. One of the names, Zaclir, was thought to sound like the proposed name 'Zyclara.' The remaining name, Aldara, was thought to look and sound similar to the proposed name 'Zyclara'.

Additionally, DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of April 28, 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 Zyclara.

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***

For the study conducted on April 28, 2009, a total of 21 practitioners responded but none of the responses overlapped with any existing or proposed drug names. Only four of the participants interpreted the drug name correctly as "Zyclara", with correct interpretation occurring in both the inpatient and outpatient written studies. The remainder of participants misinterpreted the drug name. The participants in the verbal study misinterpreted the drug name as Cyclera and Diclera respectively. The majority of misinterpretations in the written studies involved the letters 'cl' being misinterpreted as 'd' and the letters 'ara' being misinterpreted as 'arn', 'arnn' and 'ar'. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

#### ***3.1.4 Comments from the Division of Dermatological and Dental Products***

Prior to beginning our evaluation on April 22, 2009, DMEPA met with the Division of Dermatological and Dental Products to discuss the Applicant's nomenclature plan, proposing a new tradename, Zyclara, for the new 3.75% strength cream (NDA 22-483). During this meeting, the Division expressed concerns with the Applicant's proposal to designate a new proprietary name for the new 3.75% strength of Imiquimod cream, citing safety concerns surrounding the potential for concomitant therapy in patients treated for varying dermal conditions for which Imiquimod cream is indicated. The Division reviewed potential clinical implications of systemic overexposure to Imiquimod that could occur if patients inadvertently administered the product prescribed under two

different proprietary names (Zyclara and Aldara). Adverse events from systemic exposure cited from the product labeling included headache, upper respiratory tract infections, influenza-like symptoms and myalgia. Additionally, the Division discussed the Applicant's future plan to study additional indications for the pending 3.75% strength which would compound product confusion if Imiquimod has two proprietary names for each strength. Both DMEPA and the Division concurred that the 3.75% and 5% Imiquimod Cream would best be managed under the same proprietary name, Aldara, with combined package insert labeling for both strengths.

DMEPA notified the Division of Dermatological and Dental Products after the draft completion of our review on May 11, 2009, to review safety concerns with the Applicant's proposed proprietary name, Zyclara, and seek additional comments. The Division concurred with our assessment that the proposed proprietary name would contribute to medication errors associated with the potential for concomitant therapy with both 'Zyclara' and 'Aldara' in patient populations being treated for one or more of the three Imiquimod indications of actinic keratosis, basal cell carcinoma and genital warts.

### ***3.1.5 Adverse Events Reporting System (AERS) Database Search***

A total of 19 medication error cases were identified in OSE Review #2006-785 (pending).\*\*\* Thirteen cases were domestic and six were foreign. Seven of the 19 cases reported two medication errors so in total, 26 medication errors were identified from the 19 cases. These errors were categorized as follows: wrong frequency (n=12), wrong technique (n=12), and wrong drug (n=2). The errors are described by type below.

- Wrong frequency (n=12): The 12 wrong frequency medication errors included 10 cases of applying the drug more often than prescribed or recommended for the condition being treated, two cases of administering the cream on the wrong days of the week. Four of the wrong frequency medication errors involved the prescriber writing the wrong frequency on the prescription; five cases involved the patient applying the cream more often than prescribed; one case involved the product being mislabeled with the wrong frequency of use when dispensed and two cases of did not specify a reason for the wrong frequency of administration.
- Wrong technique (n=12): Eight of the errors involved application of the drug to an unaffected area with the majority of these cases involving inadvertently applying or transferring the product to an unaffected area (i.e. rubbed in to the eye or touching the skin of other areas of the face) after application of the cream. In some cases, the patient admitted not washing hands thoroughly after applying the cream to the affected area. Two errors involved leaving the cream on for longer than prescribed although the reports did not specify the reason for the error. The two remaining cases involved application of more than the recommended amount of the product.
- Wrong drug (n=2): These two cases involved the reporter citing potential name confusion between Alora and Aldara, especially since they are both topical products, although no actual medication errors occurred.

### **3.1.6 Aldara Drug Utilization Analysis**

The Drug Utilization Analysis performed for this review reported both Aldara prescribers by specialty, indication of drug use and supplementary information about concurrent conditions associated with use from 2004 through 2008. The majority of prescriptions dispensed for Aldara cream were prescribed by Dermatology with 44% followed by General Practice/Family Medicine/Doctor of Osteopathy and Ob/Gyn with 13% and 9%, respectively, in year 2008. Less than 1% of prescriptions dispensed for Aldara<sup>®</sup> (Imiquimod) cream were prescribed by Oncology for the entire review period. (See Appendix H for prescribers specialty type).

According to office-based physician practices in the U.S., “Viral Warts” (ICD-9 078.1) was the top diagnosis code associated with the use of Aldara<sup>®</sup> (Imiquimod) cream approximately 70% for calendar year 2008. The second most common use for Aldara<sup>®</sup> (Imiquimod) cream was “Actinic Keratosis” (ICD-9 702.0) approximately 10% for the same period.

The Division of Epidemiology also examined concurring conditions to see what other conditions were being treated with the primary condition at the same office visit. During calendar years 2004 through 2008, when Aldara<sup>®</sup> (Imiquimod) cream was reported for the use of “Viral Warts” (ICD-9 078.1), approximately 84% of the time this condition was the only associated diagnosis code. For the same time period, when Aldara<sup>®</sup> (Imiquimod) cream was reported for the use of “Actinic Keratosis” (ICD-9 702.0), approximately 80% of the time office-based physicians reported this condition as the only associated diagnosis code. Approximately 5% of the time “Malig NEO Skin NOS” (ICD-9 173.9) was reported as a concurrent condition with “Actinic Keratosis” (ICD-9 702.0). Conversely, “Actinic Keratosis” (ICD-9 702.0) was reported as a concurrent condition approximately 6% of the time when “Malig NEO Skin NOS” (ICD-9 173.9) was the primary condition.\*\*\*<sup>8</sup>

### **3.1.7 Safety Evaluator Risk Assessment**

#### **3.1.7.1 Names Identified For Orthographic and Phonetic Similarity to the Proposed Name**

Independent searches by the primary Safety Evaluator identified four additional names which were thought to look similar to Zyclara and represent a potential source of drug name confusion. These names include Antara, Mycelex, Myleran and Zemplar.

Thus, a total of twenty-one names were analyzed to determine if the drug names could be confused with Zyclara and if the drug name confusion would likely result in a medication error.

Failure mode and effect analysis (FMEA) was then applied to determine if the potential name could potentially be confused with any of the twenty-one names and lead to medication errors. This analysis determined that the name similarity between Zyclara

---

<sup>8</sup> OSE Review 2009-487: Total Dispensed Prescriptions by Physician Specialty, Indications for Use, and Concurrent Conditions associated with use for Aldara. Patty Greene, Division of Epidemiology, May 8, 2009.

and the 21 names identified was unlikely to result in medication errors for the reasons presented in Appendices D through G.

However, our analysis found that the Applicant's proposal to introduce a new tradename, Zyclara, for their 3.75 % Imiquimod product presents a safety risk of product overdose medication errors if patients inadvertently receive concomitant treatment with both products, unaware that 'Aldara' and 'Zyclara' are the same product varying only in strength. The safety risks associated with such medication errors can lead to system overexposure of Imiquimod causing adverse events documented in Imiquimod labeling including headache, upper respiratory infection, influenza-like symptoms and myalgia.

### **3.1.7.2 Applicant Justification for Labeling Separate from Aldara**

The Applicant states that their Imiquimod 3.75 % strength product would best be managed with separate labeling (package insert labeling) and a different proprietary name (Zyclara) to distinguish the products features from currently marketed Aldara 5 % cream. They believe that the different strengths, different dosing regimen and field of treatment warrant separate labeling and separate brand name in the best interest of the patient to ensure the drug will be used correctly. The Applicant believes that these differentiating attributes represent significantly more than "just a different strength of an existing product". They are also concerned that medication errors will occur if both products are contained within the same package insert, since "combining labeling creates a context in which dosing instructions for the new product can mistakenly be connected with the approved product."

The Applicant discusses the varying indications of use between the 3.75 % and 5 % Imiquimod products and the potential for medication errors between the two products if the wrong strength is applied and/or the wrong dosing regimen is used, citing adverse events that could occur with excessive application of the product which could lead to a severe inflammatory reaction and increase the risk of systemic adverse events such as flu-like illness. They further discuss that by combining both products in the same package insert could increase the frequency of dispensing errors (dispensing 3.75 % versus 5 %, or vice-versa). They conclude that having separate package inserts and separate brand names for the two products will reduce the risk of dosing and dispensing errors.

The Applicant believes that adverse event tracking will be challenging if both product strengths are managed under the same tradename with a single label stating "with all indications and strengths combined on a single label, and under the same brand name (Aldara) it might be very easy for those reporting adverse events simply to write 'Aldara' on the MedWatch form or adverse event report form without distinguishing the strength, and without indicating which dosing regimen and application instructions were being used." They explain that separate brand names and separate package inserts will increase likelihood of practitioner and patient recognition of the correct product to distinguish and differentiate them more accurately during adverse event reporting.

Finally, the Applicant cited 'Agency Precedent' for separate labeling and separate brand names including Differin, MetroGel, Olux, Temovate, Lidex, and Diprolene as having separate labeling, and products including Wellbutrin versus Zyban, Zometa versus

Reclast, Proscar versus Propecia, and Tazorac versus Avage, as products with the same active ingredient but with different proprietary names.

#### **4 DISCUSSION**

Zyclara is the proposed proprietary name for Imiquimod Cream, 3.75 %. This product is currently marketed by the manufacturer under the proprietary name, Aldara. Aldara is a 5 % cream whereas Zyclara is a 3.75 % cream. Additionally, the indications for use are slightly different between the two strengths. Approval of Zyclara would represent a dual tradename for Imiquimod. The Applicant submitted rationale for the use of a dual tradename and this information was subsequently evaluated with the DDDP clinical team.

Our evaluation of the proposed proprietary name, Zyclara (Imiquimod Cream 3.75 %) also considered comments from DDMAC, the DDDP clinical team and DMEPA. DDMAC did not have concerns with the proposed proprietary name. DMEPA identified twenty-one names as having some similarity to the proposed name, Zyclara. Both DMEPA and DDDP have concerns with marketing this product under two proprietary names.

DMEPA's FMEA indicated that the proposed name is not likely to result in name confusion that could lead to medication error due to orthographic or phonetic similarities with the names. However, our analysis determined that the Applicant's proposal for a different tradename 'Zyclara' will create a safety risk for inadvertent concomitant therapy in same-patient populations being treated with 'Zyclara' and 'Aldara'. This finding is supported by the DDDP clinical team. Additionally, our analysis found that the potential for product confusion and medication errors identified in the Applicant's Justification for Separate Labeling could occur independent of different tradenames between the two Imiquimod strengths and therefore, do not support the necessity for a separate tradename for the 3.75 % strength, as our recent post-marketing analysis of Aldara medication errors identified wrong frequency and wrong technique medication errors unrelated to product labeling for the currently marketed product. Our rationale is discussed below.

##### **4.1 IMIQUIMOD DOSING REGIMEN**

The Applicant states that using two different proprietary names for the Imiquimod strengths will avert medication errors due to the diversity in dosing regimens between the two strengths. We disagree with the Applicant's rationale that assigning different proprietary names to each strength will avert these types of medication errors since confusion surrounding the complexity of dosing and administration and treatment regimen are unrelated to the product name, but rather, as indicated in the medication error AERS cases reviewed for Aldara, are elements of the complexity of the treatment regimen that need to be differentiated in clear, defined labeling. DMEPA acknowledges that if the Imiquimod insert labeling instructions are not referenced appropriately for the desired strength and for the desired indication, the potential for medication errors exists during prescribing, dosing, dispensing and administering the drug. This potential for error is compounded by the fact that both medications are indicated for 'actinic keratosis' and the relative complexity of the dosage and administration instructions (treatment area, frequency of use, and treatment duration). DMEPA believes that these potential

medication errors could occur independent of the designation of two separate tradenames for each strength.

#### **4.2 RISK OF CONCOMITANT THERAPY**

DMEPA and DDDP believe that having two different proprietary names introduces an added safety risk of inadvertent concomitant therapy if ‘Zyclara’ and ‘Aldara’ are prescribed to the same patient by different providers. It is possible that certain patients may be treated by different providers for different conditions. The three indications of use for which Imiquimod are approved are likely to overlap in similar patient populations since it is documented in the literature that a variety of dermatologic nonmelanoma skin cancers are prevalent in certain populations with risk factors including fair skin, sun exposure, male gender, advancing age and presence of solar keratosis.<sup>9</sup> Patients could be treated for basal cell carcinoma by a dermatologist or oncologist, while they are being treated for actinic keratosis by their internal medicine provider. If the 3.75 % and 5 % Imiquimod creams are managed under separate tradenames, the potential exists that a patient is treated with Imiquimod by more than one provider, for example, a patient could be prescribed Zyclara 3.75 % for actinic keratosis and Aldara 5% for basal cell carcinoma. This concomitant therapy could go undetected by the treating physicians, the dispensing pharmacist(s) and most importantly, by the patient, who may be unaware that ‘Aldara’ and ‘Zyclara’ represent a product containing the same ingredient. By unknowingly treating both conditions simultaneously with the same active ingredient, there is a safety risk of systemic exposure to Imiquimod, which the Division cites from product labeling, include headache, upper respiratory infections, influenza-like symptoms and myalgia.

Additionally, Aldara and Zyclara have an overlapping indication of use, actinic keratosis. It is possible that a patient may be treated for the same indication of use by different prescribers. The use of the same active ingredient may go undetected because the dosing regimen for this indication of use is different between products. Aldara recommends a twice weekly application whereas Zyclara recommends a daily application at bedtime. The over use of Imiquimod could increase the occurrence of adverse reactions already associated with Imiquimod use including localized skin reactions.

Additionally, our drug utilization data analysis revealed that a variety of provider types prescribe Aldara. This information supports DMEPA’s concern with the potential for inadvertent concomitant therapy if different providers prescribe the same patient Aldara and Zyclara. The data collected regarding indication of use and concurrent conditions associated with Aldara are also informative in terms of showing the most frequent conditions Aldara is used to treat as well as illustrating that there are a proportion of Aldara users (5 % and 6 % respectively) who present with the dual diagnoses of Skin Malignancies and Actinic Keratosis. Though this proportion is small in terms of the percentage of patients who have both conditions, the data does support the safety concern DMEPA and DDDP have cited for the potential that a patient with more than one of the

---

<sup>9</sup> Angelik, I., et al. The Prevalence of Human Paspillomavirus Genotypes in Nonmelanoma Skin Cancers of Nonimmunosuppressed Individuals Identifies High-Risk Genital Types as Possible Risk Factors. *Cancer Research* 63, 7515-7519, November 1, 2003.

Imiquimod indications of use is treated for both conditions (by different providers), and inadvertently receives concomitant therapy with both Aldara and Zyclara.

Recently, the Institute for Safe Medication Practices (ISMP) highlighted medication errors that occur when a drug is marketed under more than one proprietary name, especially when one of those names is already well established. In one case, they cite a patient who was taking Revatio (Sildenafil) tablets went to the emergency room for ischemic chest pain. Emergency room staff who obtained the patient's medication history did not recognize that Revatio (better known as Viagra) contained Sildenafil, and the patient was subsequently given nitroglycerin intravenously, which is contraindicated in patients taking Sildenafil. An internist stopped the nitroglycerin drip upon realizing that Revatio contained Sildenafil, and the patient did not experience any adverse events from this error but could have been at risk for hypotension since both Sildenafil and Nitroglycerin have a vasodilating effect on the circulatory system. Viagra has received widespread professional and direct-to-consumer advertising, including the contraindications associated with nitrate use. If the patient's medical records had listed the name 'Viagra' in this situation, emergency room staff may have recognized the risk of administering nitroglycerin and avoided the medication error. ISMP also cites other dual tradenames as an ongoing source of medication errors in the clinical setting, including Zyban/Wellbutrin, Propecia/Proscar and Sarafem/Prozac. Additionally, they note that when the drugs are prescribed by different providers, dispensed by different pharmacies or when a physician prescribes the product by its generic name and it is dispensed and labeled by its brand name (e.g. Coumadin or Jantoven for a patient already taking Warfarin), the potential for medication errors is compounded even more.<sup>10</sup> Aldara was approved in February 1997 and therefore, is a well established product that providers are familiar with by name. Dual tradename product confusion could potentially occur if two proprietary names are assigned to Imiquimod causing a safety risk if patients are concomitantly treated with both 'Aldara' and 'Zyclara' by different providers, unaware that the two products contain the same active ingredient.

### **4.3 VARYING TREATMENT REGIMENS**

The Applicant provided justification for separate labeling, including a new tradename, for their 3.75 % strength Imiquimod product, citing variations in the two treatment regimens, indications of use, treatment areas, frequency of use and duration of use. DMEPA acknowledges that these variations are important to delineate in labeling however, we believe the two products can effectively be managed under one proprietary name in a combined package insert. AERS cases identified for Aldara indicated that confusion with the Imiquimod treatment regimen occur under current product labeling, varying from patient non-compliance or confusion with treatment regimen to human error involving the transfer of the product to other areas of the body. None of the cases cited lack of clarity in product labeling or patient instructions as the cause of the wrong frequency or wrong technique medication error occurrences. There is no indication, therefore, the Applicant's rationale for two separate package inserts will minimize such human factor

---

<sup>10</sup> The Institute for Safe Medication Practices. "Revatio=Sildenafil=Viagra". January 2009.

errors or avert future errors of the same type with the assignment of two proprietary names with two package inserts.

#### **4.4 PAST AGENCY PRECEDENCE FOR DUAL TRADENAME DECISIONS**

DMEPA recognizes Agency precedence that some products in the past have been approved with different proprietary names. In some cases, DMEPA did not review the proposed proprietary name therefore, we cannot comment on Agency decisions made for those products. Although DMEPA did not review the proposed proprietary name, Wellbutrin with the original new drug application, or the proposal to assign a second tradename, Zyban, for the Bupropion Hydrochloride, in 2002 our post-marketing surveillance of medication errors identified confusion between Wellbutrin and Zyban, which we reviewed in our OSE Review #02-0166\*\*\*. These cases involved incidences where patients were prescribed both drugs, causing seizures and hospitalizations, cases involving allergic reactions to the active ingredient because patients were unaware that the different proprietary name 'Zyban' contained the active ingredient Bupropion Hydrochloride, and other cases involving concomitant anti-depressant therapy with Celexa and Zyban, for different indications. DMEPA's evaluation of these cases included recommendations that the Applicant consider managing both products under the same tradename, Wellbutrin, as well as the initiation of an educational campaign.

In the case of Reclast\*\*\* and Zometa\*\*\*, DMEPA originally evaluated proposed name Zometa in 2001 and found the name acceptable. DMEPA also evaluated the proposal to assign a dual tradename, Reclast in 2004 (OSE #04-0133)\*\*\* and objected to the proposal to assign a second tradename due to the potential for product and dose confusion. DMEPA also reviewed the proposal for a second tradename for the product Tazorac in 2002 when the Applicant proposed the tradename, Prevage, for Tazarotene Cream. In this case, DMEPA also opposed the Applicant's proposal for a second tradename for similar reasons surrounding the risk of product confusion and increased potential for medication errors.\*\*\*

#### **4.5 POTENTIAL FOR PRODUCT EXTENSION AND FUTURE AVAILABILITY OF GENERICS**

We understand through discussions with DDDP that the Applicant is currently studying Imiquimod 3.75 % for (b) (4). Since the pending application for 3.75 % Imiquimod for actinic keratosis includes a different treatment regimen than the 5 % strength cream approved under the name Aldara, it is conceivable that treatment regimens will vary between strengths for (b) (4). This introduces an additional concern for the potential proposal and introduction of another proprietary name for Imiquimod, or the possibility of having two proprietary names, Zyclara and Aldara, with two overlapping indications of use. This could potentiate more product confusion and increase the possibility of similar types of wrong strength, wrong administration, wrong frequency, wrong duration of treatment, and overdose medication errors from inadvertent concomitant therapy. For example, if both the 3.75 % strength

(b) (4)

## 5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Zyclara, is vulnerable to name confusion that could lead to medication errors. Specifically, the Division of Medication Error Prevention and Analysis finds that the Applicant's proposal to use two different tradenames (Zylcara and Aldara) for Imiquimod cream presents a safety risk associated with potential concomitant treatment which could occur in patients being treated for more than one indications (actinic keratosis, superficial basal cell carcinoma and/or genital warts) by different prescribing providers, resulting in the potential for overdose of drug medication errors that could cause increased system exposure to the active ingredient, Imiquimod. Such concomitant treatment may also increase the potential for adverse reactions and local skin reactions seen with the use of Imiquimod.

### 5.1 COMMENTS TO THE APPLICANT

We have completed our review of this proposed proprietary name and have concluded that this name is not acceptable for the following reason:

Your proposal to use a different proprietary name, Zyclara, for a product containing the same active ingredient, Imiquimod cream, contained in another product you market, Aldara (Imiquimod Cream 5%) introduces an added safety risk of inadvertent concomitant therapy in patients being treated by different providers for different dermatologic conditions. The three indications of use for which Imiquimod is approved (actinic keratosis, superficial basal cell carcinoma, and external genital warts) can co-occur in individual patients. This concomitant therapy could go undetected by the treating physicians, the dispensing pharmacist(s) and most importantly, by the patient, who may be unaware that 'Aldara' and 'Zyclara' contain the same active ingredient. By unknowingly treating both conditions simultaneously with the same active ingredient, there is a safety risk of systemic exposure to Imiquimod, which may result in the following adverse events cited in the approved product labeling: headache, upper respiratory infections, influenza-like symptoms and myalgia. Additionally, Aldara and Zyclara have an overlapping indication of use, actinic keratosis. It is possible that a patient may be treated for the same indication of use by different prescribers. The use of the same active ingredient may go undetected because the dosing regimen for this indication of use is different between products. Aldara recommends a twice weekly application whereas Zyclara recommends a daily application at bedtime. In either scenario, the over use of Imiquimod could increase the occurrence of adverse reactions already associated with Imiquimod use including localized skin reactions.

Additionally, our evaluation determined that the potential for product confusion and medication errors identified in your justification for separate labeling is unfounded. The rationale for separate labeling cited variations in the two treatment regimens, indications of use, treatment areas, and frequency of use and duration of use as reasons to support the use of a different name. The errors you have described in support of the use of a different proprietary name already exist with your currently marketed product. Thus these errors

could occur independent of the use of different proprietary names between the two Imiquimod strengths.

We note that you have proposed an alternate proprietary name, (b) (4) in your submission dated March 13, 2009. However, based on the findings of this review, (b) (4) will also be unacceptable for the aforementioned reasons. We request that you submit revised labels and labeling that reflects the proprietary name Aldara and product information for both the 0.5% and 0.375% strengths.

## 6 REFERENCES

### Reviews

1. *OSE review # 2006-785, Post-marketing Review of Aldara, conducted by Loretta Holmes, Pharm.D.; Review in draft.*
2. *OSE review #2009-487-Drug Utilization Analysis, Total dispensed prescriptions by physician specialty, indication for use, and concurrent conditions associated with use for Aldara.*

### DATABASES

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

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

2. *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.

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

Drug Facts and Comparisons is a compendium organized by therapeutic course; it 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>)**

The FDA Orange Book provides a compilation of approved drug products with therapeutic equivalence evaluations.

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

USPTO provides information regarding patent and trademarks.

**9. Clinical Pharmacology Online ([www.clinicalpharmacology-ip.com](http://www.clinicalpharmacology-ip.com))**

Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It also provides a keyword search engine.

**10. Data provided by Thomson & Thomson’s SAEGIS™ Online Service, available at ([www.thomson-thomson.com](http://www.thomson-thomson.com))**

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and proprietary 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](http://www.naturaldatabase.com))**

Natural Medicines 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](http://www.statref.com))**

Stat!Ref contains full-text information from approximately 30 texts; it 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>)**

USAN Stems List contains all the recognized USAN stems.

**14. Red Book Pharmacy’s Fundamental Reference**

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

**15. Lexi-Comp ([www.lexi.com](http://www.lexi.com))**

Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

**16. Medical Abbreviations Book**

Medical Abbreviations Book contains commonly used medical abbreviations and their definitions.

**17. Adverse Events Reporting System (AERS)**

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post-marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

**18. SDI, LLC: Vector One®: National (VONA)**

SDI's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over (b) (4) prescription claims per year, representing over (b) (4) unique patients. Since 2002 Vector One® has captured information on over (b) (4) representing (b) (4) unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

**19. SDI, LLC: Physician Drug & Diagnosis Audit (PDDA)**

SDI's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from approximately 3,100 office-based physicians representing 29 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

SDI uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

**20. IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail**

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

## APPENDICES

### Appendix A:

DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA also compares 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 examines 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 even dissimilarly spelled drug name pairs to appear very similar to one another. The similar appearance of drug names when scripted has led to medication errors. The medication error staff applies expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g., “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 Table 1 below for details). In addition, the medication error staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. If provided, DMEPA will consider the Applicant’s intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Applicant has little control over how the name will be spoken in clinical practice.

**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"> <li>Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication</li> <li>Names may look similar when scripted and lead to drug name confusion in written communication</li> </ul>
	Orthographic similarity	Similar spelling Length of the name Upstrokes Downstrokes Cross-strokes Dotted letters Ambiguity introduced by	<ul style="list-style-type: none"> <li>Names may look similar when scripted, and lead to drug name confusion in written communication</li> </ul>

		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"> <li>Names may sound similar when pronounced and lead to drug name confusion in verbal communication</li> </ul>

**Appendix B:** Zyclara Letters with possible orthographic or phonetic misinterpretation

Letters in Zyclara	Scripted may appear as	Spoken may be interpreted as
Capital 'Z'	B, L, M, Q, N or lower case 't'	S or X
Lower case 'z'	v, g, y or j	S or X
lower case 'y'	g, z or j	'i' sound or any vowel sound
lower case 'c' and 'cl'	a, e, i, or l d	k
lower case 'l'	e, t or i	
lower case 'a'	o, u or e	any vowel sound
lower case 'r'	i, e, v, n or m	'err'

**Appendix C:** FDA Prescription Study for Zyclara

<b>Inpatient Medication Order</b>	<b>Outpatient Prescription</b>	<b>Voice Prescription</b>
Zyclara	Zyclara	Cyclera
Zyclara	Zydar	Diclera
Zyclara	Zydara	
Zydara	Zydarn	
Zydara	Zydarn	
Zydara		

**Appendix D:** Proprietary names used only in Foreign Countries

<b>Proprietary Name</b>	<b>Similarity to Zyclara</b>	<b>Country</b>
Zycalcit	Look-Alike	Indonesia
Zyclorax	Look-Alike	Indonesia
Zydalis	Look-Alike	Indonesia
Lyclear	Look-Alike	Canada

**Appendix E:** Drug names with no numerical overlap in dose or strength

<b>Product name with potential for confusion</b>	<b>Similarity to Proposed Proprietary Name</b>	<b>Strength and Dosage Form</b>	<b>Usual Dose (if applicable)</b>
Zyclara		3.75 % Cream	Apply once daily to skin of affected area
Antara	Look-Alike	43 mg and 130 mg Capsules	43 mg to 130 mg once daily depending on indication of use
Lyricea	Look-Alike	25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg Capsules	50 mg to 600 mg two to three times daily depending on indication of use
Zemplar	Look-Alike	2 mcg/mL and 5 mcg/mL solution for injection 1 mcg, 2 mcg and 4 mcg Capsules	Injection: 0.04 mcg/kg to 0.1 mcg/kg intravenous bolus; titrate according to PTH levels Capsule: 1 mcg to 2 mcg or 2 mcg to 4 mcg once daily depending on iPTH level
Zocor	Look-Alike	5 mg, 10 mg, 20 mg, 40 mg and 80 mg Tablets	5 mg to 80 mg per day; usual starting dose is 20 mg to 40 mg once daily
Zydus*** (pending NDA 22-246 for Metoclopramide oral disintegrating tablet)	Look-Alike	5 mg and 10 mg Tablets	10 mg to 15 mg up to four times daily
Zyrtec	Look-Alike	5 mg, 10 mg Tablets and Chewable Tablets 5 mg/5 mL Oral Syrup	5 mg to 10 mg tablets or chewable tablets daily 2.5 mg (2.5 mL) once daily

**Appendix F:** Drug names with only one strength (which may be omitted) but multiple differentiating product characteristics

<b>Product name with potential for confusion</b>	<b>Strength</b>	<b>Usual Dose (if applicable)</b>	<b>Differentiating Product Characteristics</b>
Zyclara	3.75 % Cream	Apply once daily to skin of affected areas (face or balding scalp) for two 2-week treatment cycles	Dose expressed 'apply to skin of affected area' Dosage form is topical cream Route of administration is topical
Byetta	250 mcg/mL	5 mcg or 10 mcg per dose administered twice daily	Dose expressed 'X mcg' per dose Dosage form is solution for injection Route of administration is subcutaneous injection
Fludara	50 mg	25 mg/m <sup>2</sup>	Dose expresses 'X mg/m <sup>2</sup> ' or 'X mg' Dosage form is lyophilized powder for injection Route of administration is intravenous
Lysodren	500 mg	2 grams to 6 grams per day in divided doses of either three or four times daily	Dose expressed as 'X grams' or 'X tablets' Dosage form is tablet Route of administration is oral
Mycelex	10 mg	One troche five times daily for 14 days	Dose expressed 'take one' Dosage form is troche Route of administration is oral
Myleran	2 mg	4 mg to 8 mg total daily dose in one or two divided doses or 60 mcg/kg	Dose expressed 'X mg' or 'X tablets' Dosage form is tablet Route of administration is oral
Zyclorin	0.10 %	One drop in each eye twice daily	Dose expressed 'one drop' Dosage form is ophthalmic solution Route of administration is topical ophthalmic
Zydone	5 mg/400 mg	One to two tablets every four to six hours as needed	Dose expressed as 'one' or 'two' tablets Dosage form is tablet Route of administration is oral
Zymar	0.3 %	One drop every two hours into affected eye(s) days one and two; one drop up to four times daily on days three through seven	Dose expressed as 'one drop' Dosage form is ophthalmic solution Route of administration is topical ophthalmic

**Appendix G:** Look-Alike names with potential for confusion

<b>Failure Mode: Name Confusion</b>	<b>Causes (could be multiple)</b>	<b>Rationale</b>
<b>Zyclara (Imiquimod)</b>	<b>3.75 % Topical Cream</b>	<b>Apply once daily to skin of affected areas (face or balding scalp) for two 2-week treatment cycles</b>
<p>Climara (Estradiol) Transdermal Patch</p> <p>0.025 mg/day 0.0375 mg/day 0.05 mg /day 0.06 mg/day 0.075 mg/day 0.1 mg/day</p>	<p>Orthographic similarities in the names include ‘ara’ are presented in the same positions of both names and ‘i’ can look like ‘l’.</p> <p>Numeric overlap in strength (0.0375 versus 3.75) and both are topical products.</p> <p>Prescription orders may overlap with ‘use as directed’.</p>	<p>Orthographic differences in the names and application/administration instructions minimize the likelihood of medication error in the usual practice setting.</p> <p><i>Rationale:</i></p> <p>Capital ‘Z’ in Zyclara does not look like capital ‘C’ in Climara. Zyclara contains a downstroke ‘y’ in the second letter position not present in Climara, which provides orthographic distinction between the two names. Additionally, the letter ‘l’ is placed in the second letter position of Climara while it is in the fourth letter position of Zyclara.</p> <p>Although dose overlap may occur between Climara and Zyclara on prescription orders if written ‘apply’ and numeric strength overlap exists between Climara ‘0.0375 mg/day’ and Zyclara 3.75 %, prescription orders for Climara would include application site information such as “apply one patch” or “apply to abdomen or buttock” while Zyclara prescription orders would include ‘apply to affected areas’ and may also include the words ‘face or balding scalp’.</p> <p>Additionally, the unit of measure ‘%’ versus ‘mg’ may provide additional distinction on prescription orders.</p>
<p>Zaclir (Benzoyl Peroxide) 4 % and 8 % Lotion</p>	<p>Orthographic and phonetic similarities in the names include both names begin with the letter ‘Z’ and the letters ‘cl’ and ‘r’ are similarly placed. ‘Zaclir’ can sound like ‘Zyclar’ phonetically.</p>	<p>Orthographic and phonetic differences in the names, usual recommended dose and route of administration minimize the likelihood of medication error in the usual practice setting.</p> <p><i>Rationale:</i></p> <p>Zyclara has a downstroke ‘y’ in the second letter position not present in Zaclir and Zyclara appears longer with seven letters versus six letters in Zaclir. Additionally, Zyclara has three syllables ending in the vowel sound ‘a’ while Zaclir has only two syllables ending in the sound ‘ir’.</p> <p>Although there is dose overlap between the two products both written as ‘apply to skin’, Zaclir is available in two strengths (4 % and 8 %) which would be included on prescription orders, while Zyclara is available in only one strength (3.75 %) further differentiating the two names.</p>

1 page has been withheld in full immediately following this page as B4 CCI/TS

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

/s/

-----  
Cathy A Miller  
6/12/2009 04:19:07 PM  
DRUG SAFETY OFFICE REVIEWER

Kellie Taylor  
6/12/2009 04:22:17 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
6/12/2009 04:29:27 PM  
DRUG SAFETY OFFICE REVIEWER