CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

2011153Orig1s000

OTHER REVIEW(S)

SEALD LABELING REVIEW

This SEALD Labeling Review identifies major aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

APPLICATION NUMBERS	NDA 201153 & NDA 22483/S-001
APPLICANT	Graceway Pharmaceuticals, Incorporated
PRODUCT NAME	Zyclara (imiquimod) Cream
SUBMISSION DATES	February 12, 2010 (201153) June 9, 2010 (22483/S-001)
PDUFA DATES	December 12, 2010 (201153) April 9, 2011 (22483/S-001)
SEALD REVIEW DATE	March 24, 2011
SEALD LABELING REVIEWER	Debra Beitzell, BSN

The following checked Selected Requirements for Prescribing Information items are outstanding labeling issues that must be corrected before the final draft labeling is approved.

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**

☐ HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.

☐ HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.

☐ There is no redundancy of information.

☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)

☐ A horizontal line must separate the HL and Table of Contents (TOC).

☐ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.

☒ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.

(b) (4)

[redacted]

☐ Section headings are presented in the following order:

• **Highlights Limitation Statement** (required statement)
• **Drug names, dosage form, route of administration, and controlled substance symbol, if applicable** (required information)
• **Initial U.S. Approval** (required information)
• **Boxed Warning** (if applicable)
• **Recent Major Changes** (for a supplement)
• **Indications and Usage** (required information)
• **Dosage and Administration** (required information)
• **Dosage Forms and Strengths** (required information)
• **Contraindications** (required heading – if no contraindications are known, it must state "None")
• **Warnings and Precautions** (required information)
• **Adverse Reactions** (required AR contact reporting statement)

• **Drug Interactions** (optional heading)
• **Use in Specific Populations** (optional heading)
• **Patient Counseling Information Statement** (required statement)
• **Revision Date** (required information)

- **Highlights Limitation Statement**

  ☒ Must be placed at the beginning of HL, **bolded,** and read as follows: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**." (b) (4)

  [redacted]

- **Product Title**

  ☐ Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

  ☐ The verbatim statement "Initial U.S. Approval" followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

  ☐ All text in the boxed warning is **bolded**.

  ☐ Summary of the warning must not exceed a length of 20 lines.

  ☐ Requires a heading in UPPER-CASE, **bolded** letters containing the word "**WARNING**" and other words to identify the subject of the warning (e.g.,"**WARNING: LIFE-THREATENING ADVERSE REACTIONS**").

  ☐ Must have the verbatim statement "***See full prescribing information for complete boxed warning***." If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

  ☐ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

  ☒ The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, "Dosage and Administration, Coronary Stenting (2.2) --- 2/2010." (b) (4)

  [redacted]

- ☒ For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line ("margin mark") on the left edge. Please insert margin marks in I&U, D&A, and W&P sections of FPI.
- ☐ A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
- ☐ Removal of a section or subsection should be noted. For example, "Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010."

- **Indications and Usage**
  - ☐ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)]." Identify the established pharmacologic class for the drug at:

    http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm.

    Imiquimod does not have an established pharmacologic class at this time.

- **Contraindications**
  - ☐ This section must be included in HL and cannot be omitted. If there are no contraindications, state "None."
  - ☐ All contraindications listed in the FPI must also be listed in HL.
  - ☐ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
  - ☐ For drugs with a pregnancy Category X, state "Pregnancy" and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**
  - ☐ Only "adverse reactions" as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
  - ☐ For drug products other than vaccines, the verbatim **bolded** statement, "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or FDA at 1-800-**

FDA-1088 or www.fda.gov/medwatch" must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

  ☐ Must include the verbatim statement: "**See 17 for Patient Counseling Information**" or if the product has FDA-approved patient labeling: "**See 17 for Patient Counseling Information and (insert either "FDA-approved patient labeling" or "Medication Guide")**.

- **Revision Date**

  ☐ A placeholder for the revision date, presented as "Revised: MM/YYYY or Month Year," must appear at the end of HL. The revision date is the month/year of application or supplement approval. Insert month of revision date upon approval of supplement.

Contents: Table of Contents (TOC)

☐ The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.

☐ The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.

☐ All section headings must be in **bold** type, and subsection headings must be indented and not bolded.

☐ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:

8.1 Pregnancy

8.3 Nursing Mothers (not 8.2)

8.4 Pediatric Use (not 8.3)

8.5 Geriatric Use (not 8.4)

☐ If a section or subsection is omitted from the FPI and TOC, the heading "**Full Prescribing Information: Contents**" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI)

- **General Format**

- ☐ A horizontal line must separate the TOC and FPI.
- ☐ The heading **FULL PRESCRIBING INFORMATION** must appear at the beginning in UPPER CASE and **bold** type.
- ☐ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**
  - ☐ Must have a heading, in UPPER CASE, **bold** type, containing the word "**WARNING**" and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
  - ☐ Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**
  - ☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**
  - ☐ Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided.
  - ☐ For the "Clinical Trials Experience" subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

    "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."
  - ☐ For the "Postmarketing Experience" subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

    "The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

- **Use in Specific Populations**
  - ☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**
  - ☐ This section is required and cannot be omitted.
  - ☐ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement "See FDA-approved patient labeling (insert type of patient labeling)." should appear at the beginning of Section 17 for prominence. For example:
    - "See FDA-approved patient labeling (Medication Guide)"
    - "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
    - "See FDA-approved patient labeling (Patient Information)"
    - "See FDA-approved patient labeling (Instructions for Use)"
    - "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

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

/s/

DEBRA C BEITZELL
03/24/2011

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

*****Pre-Decisional Agency Information*****

Date: November 5, 2010

To: NDA 201153 and NDA 22483 Supplement-1

From: Christine Corser, Pharm.D., Regulatory Review Officer
Division of Drug Marketing, Advertising and Communications

Sheetal Patel, Pharm.D., Regulatory Review Officer
Division of Drug Marketing, Advertising and Communications

Subject: Zyclara (imiquimod) cream 3.75%
NDA 201153

The DDMAC labeling review for NDA 201153 that was entered into DARRTS on 09/27/2010 is also the DDMAC labeling review for NDA 22483 Supplement-1.

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

/s/

CHRISTINE G CORSER
11/05/2010

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Dermatology and Dental Products

Application Number: NDA 201153

Name of Drug: Zyclara (imiquimod) Cream, 3.75%

Applicant: Graceway Pharmaceuticals, Inc.

Material Reviewed:

Submission Date(s): June 8, 2010

Receipt Date(s): June 8, 2010

PDUFA Due Date: December 12, 2010

Submission Date of Structure Product Labeling (SPL): June 8, 2010

Type of Labeling Reviewed: PLR Labeling

Background and Summary

NDA 201153, Zyclara (imiquimod) Cream, 3.75%, submitted February 5, 2010 is indicated for the topical treatment of clinical typical, visible pr palpable actinic keratoses (AK) of the full face or balding scalp in immunocompetent adults and external genital and perianal warts/condyloma acuminate in patients 12 years or older. This application was submitted as a 505(b)(1).

While Zyclara (imiquimod) Cream, 3.75% is a new formulation for external genital and perianal wasrt/condyloma acuminate in patients 12 years or older, imiquimod is already an approved drug in the US and marketed as Aldara (imiquimod) Cream, 5% for this indication.

Review

This review provides a list of formatting revisions for proposed labeling. These comments are based on 21 CFR 201.1 and FDA recommendations to provide labeling quality and consistency across review divisions. When a reference is not cited, consider the comment as a recommendation only.

The following issues/deficiencies have been identified in the proposed labeling.

Highlights Section:

1. According to 21 CFR 201.57(d)(9), a recent major changes section should be added for new indication in the Indications and Usage section.

2. Remove bolding from "ZYCLARA" in the Indications and Usage section.

3. Add a reference to "Avoid concomitant use of Zyclara Cream and any other imiquimod cream." in the Warnings and Precaution section.

Full Prescribing Information: CONTENTS Section:

4. Delete (b) (4).

Full Prescribing Information (FPI) Section:

5. According to 21 CFR 201.57(d)(9), for recent major changes, the corresponding new text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge.

6. Reference the Patient Packaging Insert (PPI) in the Patient Counseling Information section.

Recommendations

The labeling deficiencies/issues identified above should be included in the labeling that will be conveyed to the applicant.

_____
Nichelle Rashid
Regulatory Project Manager

Supervisory Comment/Concurrence:

_____
Barbara Gould
Chief, Project Management Staff

Drafted: NER/07/08/10
Revised/Initialed: NER 10/04/10; B. Gould 10/8/2010
Finalized: NER 10/08/10
Filename: Labeling Review (initial PLR).doc

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

/s/

NICHELLE E RASHID
10/13/2010

BARBARA J GOULD
10/15/2010

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:	October 7, 2010
Application Type/Number:	NDA 201153 NDA 022483
To:	Susan Walker, MD, Director Division of Dermatological and Dental Products
Through:	Zachary Oleszczuk, PharmD, Team Leader Denise Toyer, PharmD, Deputy Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Cathy A. Miller, MPH, BSN, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Zyclara (Imiquimod) Cream 3.75%
Applicant/sponsor:	Graceway Pharmaceuticals
OSE RCM#:	2010-1279-1

CONTENTS

1 INTRODUCTION

This review is written in response to a request from DDDP for DMEPA to re-evaluate the revised carton labeling and package insert labeling submitted on August 26, 2010.

2 REGULATORY HISTORY

The Division of Medication Error Prevention and Analysis reviewed proposed container labels, carton labeling and package insert labeling for NDA 201153 Zyclara (Imiquimod) in OSE Review #2010-1279 dated August 19, 2010. In our review, we made recommendations for revisions to carton labeling to remove the statements (b) (4) (b) (4), due to varying dosage regimens requiring that more than one sachet (packet) be administered for a single dose.

During an internal Zyclara labeling meeting dated September 29, 2010, it was brought to DMEPA's attention that revised labels and labeling had been submitted by the Applicant in a subsequent submission dated after the completion of our review which reflected our recommendations, however, DMEPA had not been consulted to re-evaluate the revisions. DDDP requested that DMEPA re-evaluate the revised labels and labeling to assure the Applicant had addressed our previous recommendations.

3 METHODS AND RESULTS

DMEPA used Human Factors and Failure Mode and Effects Analysis (FMEA)[1] in our evaluation of carton labeling (see Appendices A and B) and package insert labeling (no image). We also evaluated the previous review OSE #2010-1279 dated August 19, 2010 to ensure that DMEPA's recommendations were implemented in the labels and labeling.

For this review, DMEPA reviewed proposed carton labeling and insert labeling submitted by the Applicant on August 26, 2010.

4 RESULTS AND CONCLUSION

The following summarizes our findings from the review of the revised carton labeling and package insert labeling.

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

4.1 COMMENTS TO THE DIVISION

1. Carton Labeling

The Applicant has adequately addressed our recommendation to remove the language (b) (4) and we have no additional comments for the carton labeling.

2. Package Insert Labeling, Dosage and Administration Section

As stated by DMEPA at the August 29, 2010 Zyclara labeling meeting, we recommend a statement be added clarifying that only one Zyclara packet should be used per administration for the External Genital Warts indication. Zyclara is also indicated for the treatment of Actinic Keratosis and the dosing instructions for this indication state that 'Up to two packets of Zyclara Cream may be applied to the treatment area at each application." In order to clarify the correct dosing for the External Genital Warts indication and to help minimize the potential for wrong dose medication errors, we recommend a statement such as "only one packet of Zyclara Cream should be applied to the treatment area at each application."

5 REFERENCES

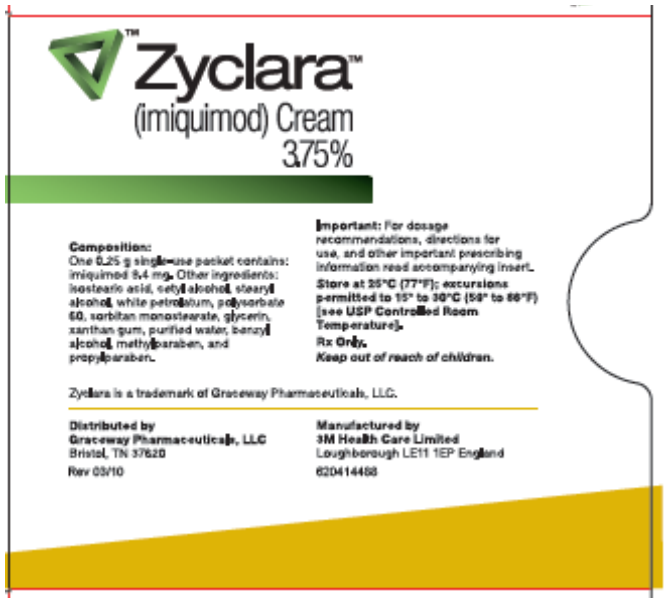
OSE Review #2009-172 dated November 4, 2009; Zyclara Labels and Labeling Review; Miller, Cathy A.

OSE Review #2010-443 dated March 24, 2010; Zyclara Revised Labels and Labeling Review; Miller, Cathy A.

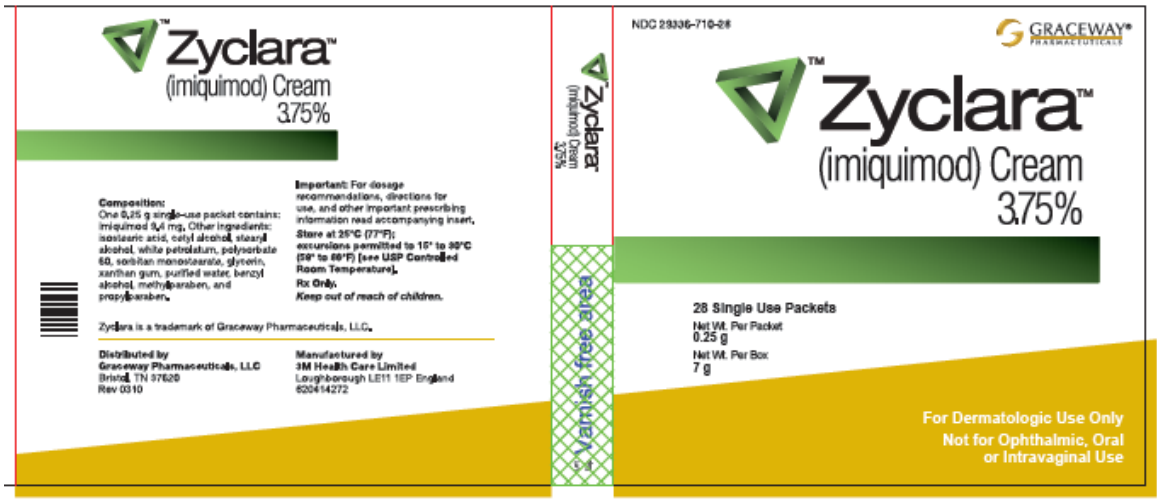
OSE Review #2010-1279 dated August 19, 2010; Zyclara Labels and Labeling; Miller, Cathy A.

APPENDICES

Appendix A: Revised Carton Labeling submitted August 26, 2010



Appendix B: Revised Fold-Out Carton Labeling submitted August 26, 2010



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
10/07/2010

ZACHARY A OLESZCZUK
10/07/2010

DENISE P TOYER
10/07/2010

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

*****Pre-Decisional Agency Information*****

Date: September 24, 2010

To: Nichelle Rashid, Regulatory Health Project Manager
Division of Dermatology and Dental Products

From: Christine Corser, Pharm.D., Regulatory Review Officer
Division of Drug Marketing, Advertising and Communications

Sheetal Patel, Pharm.D., Regulatory Review Officer
Division of Drug Marketing, Advertising and Communications

Sheila Ryan, Pharm.D., Group Leader
Division of Drug Marketing, Advertising and Communications

Subject: Zyclara (imiquimod) cream 3.75%
NDA: 201153

DDMAC has reviewed the proposed package insert (PI) and proposed patient package insert (PPI) for Zyclara (imiquimod) cream 3.75%, dated 9/1/2010, and we offer the following comments. Please feel free to contact Christine at (301)796-2653 or Sheetal at (301)796-5167 with any questions or clarifications.

28 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

SHEETAL PATEL
09/27/2010

CHRISTINE G CORSER
09/27/2010

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, 16, 2010
To:	Susan Walker, M.D., Director **Division of Dermatology and Dental Products (DDDP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Patient Labeling Reviewer, Acting Team Leader **Division of Risk Management**
From:	Latonia M. Ford, RN, BSN, MBA Patient Labeling Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling (Patient Package Insert)
Drug Name(s):	Zyclara (imiquimod) cream 3.75%
Application Type/Number:	NDA 201153
Applicant/sponsor:	Graceway Pharmaceuticals, LLC
OSE RCM #:	2010-1281

1 INTRODUCTION

This review is written in response to a request by the Division of Dermatology and Dental Products (DDDP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for Zyclara (imiquimod) Cream 3.75%.

Graceway Pharmaceuticals, LLC submitted a New Drug Application (NDA) 20-1153, for Zyclara (imiquimod) cream 3.75% on February 5, 2010. Zyclara (imiquimod) cream 3.75% is indicated for the treatment of:

- visible or palpable actinic keratoses (AK) of the full face or balding scalp in immunocompetent adults.
- external genital and perianal warts/condyloma acuminate in patients 12 years or older.

Please send these comments to the Applicant. DRISK spoke with DMEPA and a separate DMEPA review of the IFU was completed on August 19, 2010. Let us know if DDDP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

2 MATERIAL REVIEWED

- Draft Zyclara (imiquimod) cream 3.75% Prescribing Information (PI) received February 12, 2010, revised by the Review Division throughout the current review cycle and sent by the Review Division to DRISK on September 1, 2010.
- Draft Zyclara (imiquimod) cream 3.75% Patient Package Insert (PPI) received on February 12, 2010, revised by the Review Division throughout the current review cycle, and sent by the Review Division to DRISK on September 1, 2010.

3 RESULTS OF REVIEW

In our review of the PPI, we have:

- where appropriate, made the PPI consistent with the DRISK August 2010 recommendations for Aldara (imiquimod) cream PPI review provided to DDDP.
- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated PPI is appended to this memo. Any additional revisions to the PI should be reflected in the PPI.

Please let us know if you have any questions.

13 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201153	ORIG-1	GRACEWAY PHARMACEUTICALS LLC	Zyclara (Imiquimod) Cream 3.75%

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

/s/

LATONIA M FORD
09/16/2010
Zyclara (imiquimod) cream 3.75% DRISK Final PPI Review.

LASHAWN M GRIFFITHS
09/16/2010

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:	August 19, 2010
Application Type/Number:	NDA 201153
To:	Susan Walker, MD, Director Division of Dermatological and Dental Products
Through:	Zachary Oleszczuk, PharmD, Team Leader Kellie Taylor, PharmD, Associate Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Cathy A. Miller, MPH, BSN, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Zyclara (Imiquimod) Cream 3.75%
Applicant/sponsor:	Graceway Pharmaceuticals
OSE RCM#:	2010-1279

CONTENTS

1 INTRODUCTION

This review is written in response to a request from the Division of Dermatological and Dental Products for the Division of Medication Error Prevention and Analysis (DMEPA) to evaluate container labels, carton and insert labeling for areas that could lead to medication errors.

2 REGULATORY HISTORY

On December 19, 2008, the Applicant submitted new drug application (NDA 022483) for Zyclara, for the indication of the treatment of Actinic Keratoses (AK) of the full face or balding scalp in immunocompetent adults.

DMEPA reviewed and provided recommendations for Zyclara labels and labeling in OSE Review #2009-172, dated November 4, 2009.

On March 15, 2010, the Division of Dermatological and Dental Products consulted DMEPA to review revised Zyclara labels and labeling submitted in the Applicant's February 23, 2010 electronic re-submission. On March 24, 2010, DMEPA provided our recommendations for revisions to the labels and labeling in OSE Review #2010-443. Recommendations included removing reference to the words (b) (4) from the carton labeling and insert labeling, since the dosage and administration instructions allow for more than one single packet per administration and the words (b) (4) do not accurately reflect this administration.

On February 5, 2010, the Applicant submitted a second new drug application (NDA 201153), proposing an additional indication for Zyclara, for the treatment of external genital and perianal warts and condyloma acuminate in patients twelve years and older. This submission included container labels, carton labeling and insert labeling for the proposed new indication. The Applicant submitted the new application (NDA 201153) based on advice given by DDDP in a preNDA meeting between DDDP and the Applicant held on November 18, 2009. This decision was based on the fact that, at the time of the submission for NDA 201153, DDDP had not completed the review of Zyclara, new drug application (NDA 022483), for the indication of the treatment of Actinic Keratoses (AK), of the full face or balding scalp in immunocompetent adults.

On March 25, 2010, Zyclara (NDA 022483) was approved for the indication of the treatment of Actinic Keratoses (AK), of the full face or balding scalp in immunocompetent adults.

On June 7, 2010, the Applicant responded to a May 21, 2010 request from DDDP to amend the subject of their application (NDA 201153) with revised labeling to reflect both indications in one combined package insert labeling document. The Applicant submitted the revised insert labeling reflecting the proposed new indication of genital warts along with the approved indication of actinic keratoses combined into one package insert labeling document. DDDP also requested that an NDA supplement be submitted to NDA 022483 to combine the two indications in one label.

3 METHODS AND RESULTS

For this review, DMEPA searched the FDA Adverse Event Reporting System (AERS) database and reviewed proposed container labels, carton labeling and insert labeling.

3.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

Since Imiquimod is a marketed product, the Division of Medication Error Prevention and Analysis searched the Adverse Events Reporting System (AERS) database for any medication errors involving Imiquimod that may have involved label and labeling for the product. Because we conducted an AERS search of Imiquimod on August 18, 2009 in our previous labeling review of Zyclara, OSE Review #2009-172, we limited our search dates to August 18, 2009 to the July 12, 2010. We used the active ingredient "Imiquimod", the tradenames 'Aldara' and 'Zyclara' and the verbatim terms 'Aldara%', 'Zyclara%' and 'Imiquimod'. The MedDRA Higher Level Group Term (HLGT) "Medication Errors" and "Product Quality Issues" were used to perform the search.

The reports were manually reviewed and combined to determine if a medication error occurred. If an error occurred, the staff reviewed the reports to determine if the root cause could be associated with the labels or labeling of the product, and thus pertinent to this review. Those reports that did not describe a medication error or did not describe an error applicable to this review were excluded from further analysis. Duplicate reports were combined into cases. The cases that did describe a medication error were categorized by type of error.

3.2 LABELS AND LABELING

DMEPA used Human Factors and Failure Mode and Effects Analysis (FMEA)[1] in our evaluation of container labels, and carton labeling submitted on February 5, 2010 and revised insert labeling submitted on June 7, 2010 (see Appendices A through C).

4 RESULTS AND DISCUSSION

The following summarizes our findings from the AERS search and review of the proposed container labels and carton labeling.

4.1 AERS RESULTS

Our AERS search retrieved two reports between August 18, 2009 to July 12, 2010. Both reports (ISR #6342143-1 and #6335934-4) involved adverse events while using Aldara 5% cream that were not related to medication errors and therefore, were not considered relevant to our Zyclara labels and labeling review.

During our initial labels and labeling review of Zyclara, OSE Review #2009-172, DMEPA performed a search of AERS to identify medication errors associated with Imiquimod since the product was marketed under the proprietary name, Aldara, for the same indication of use. Our search identified cases that involved maladministration of

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

the product including wrong site (n 2), wrong frequency of administration and/or wrong dose (n 18) and patient non-compliance (n 1) and a patient complaint about not being provided with appropriate administration instructions by the prescriber (n 1). Although the cases identified in our search primarily involved maladministration of the product, our evaluation did not find that ambiguity in the dosage and administration for the product was cited as a contributing factor to the medication errors identified in our search.

4.2 LABELS AND LABELING

DMEPA provided recommendations for the removal of the words (b) (4) and (b) (4) (b) (4) in our OSE Review #2010-443 dated March 24, 2010. The carton labeling still contain the language on the principal display panel of the carton labeling and fold-out wallet labeling. Additionally, the insert labeling Section 2.2 contains the words (b) (4) (b) (4) in the sentence "Patients should be prescribed no more than 2 (b) (4) (56 (b) (4) for the treatment course". The labeled dosing instructions for Zyclara's actinic keratoses indication state "up to two packets of Zyclara Cream may be applied to the treatment area for each application." Because the terms (b) (4) and (b) (4) imply that only one packet is always used for one application, DMEPA found that the language was not congruent with the labeled directions and should be removed. DMEPA communicated this information to DDDP in our March 18, 2010 email communication, however, DMEPA could not determine whether these recommendations were incorporated into the product labels and labeling for approved NDA 022483 or whether the currently marketed container labels and carton labeling have this language. However we did find Zyclara container labels and carton labeling on a commonly used drug database that did not contain the language (b) (4) and (b) (4)

The carton labeling submitted for the proposed indication of genital warts included the terms (b) (4) and (b) (4) therefore, DMEPA consulted with the DDDP medical officer on July 7, 2010, in order to clarify what the dosage and administration instructions would be for the proposed genital warts indication. Per the DDDP medical officer, only one packet (one application) of Zyclara cream may be applied per daily administration for the indication of genital warts.

However, because the number of packets per application will vary depending on the indication (up to two packets for actinic keratoses versus one packet for genital warts) DMEPA still contends that the language (b) (4) and (b) (4) displayed on the carton labeling, and contained in the insert labeling, is confusing and ambiguous, since they imply 'one single dose is always one packet' and the number of Zyclara packets used per application varies depending on the indication of use. In order to minimize confusion that could lead to wrong dose medication errors, we believe this language should be removed from carton labeling and insert labeling.

DMEPA considered whether the addition of the indication for genital warts would introduce medication errors with Zyclara based on postmarketing medication error reports with Aldara, which has the same indications of use. DMEPA believes that the varying dosing and frequency of administration for different indications pose the risk of contributing to wrong dose or wrong frequency of administration medication errors. However, we believe that the dosage and administration for both indications are clearly

delineated and described in the Dosage and Administration section of the insert labeling for Zyclara. DMEPA will continue to monitor for these types of errors during our routine post-marketing surveillance efforts.

5 CONCLUSIONS AND RECOMMENDATIONS

DMEPA reviewed the Zyclara container labels, carton labeling and insert labeling for the proposed indication of genital wart. Although we do not believe that the addition of the 'genital warts' indication of use will contribute to medication errors for the product, we maintain our recommendation from OSE Review #2010-443 to remove the language (b) (4) and (b) (4) from insert labeling and carton labeling.

5.1 COMMENTS TO THE DIVISION

As DMEPA stated in our previous review of Zyclara labeling (OSE Review #2010-443), we find that the words (b) (4), and (b) (4) are ambiguous and may imply that one single dose is always one sachet and lead to dosing errors. The dosage and administration section of Zyclara states that "up to two packets of Zyclara Cream may be applied to the treatment area for each application' for actinic keratoses. Per DMEPA email communications with the DDDP medical officer, Milena Lolic, on July 7, 2010, regarding the dosage and administration for the proposed indication of genital warts, we understand that only one packet will be applied per daily application. However, because the number of packets per application will vary depending on the indication (up to two packets for actinic keratoses versus one packet for genital warts) DMEPA still contends that the language (b) (4) and (b) (4), displayed on the carton labeling, and contained in the insert labeling is confusing and could lead to wrong dose medication errors. We are requesting that the language be omitted from the insert labeling were it appears in Section 2.2 dosage and administration as follows:

A. Dosage and Administration Section 2.2

Revise the sentence (b) (4) in Section 2.2 of the insert labeling to read "Patient should be prescribed no more than 2 boxes (56 packets)."

5.2 COMMENTS TO THE APPLICANT

A. Carton Labeling

1. Remove the words (b) (4) and (b) (4) from the carton labeling. The words (b) (4) and (b) (4) are ambiguous and may imply that one single dose of Zyclara is always one sachet and lead to dosing errors. Although we acknowledge that the Zyclara dosing for the proposed indication of genital warts will be one packet per daily application, the Zyclara dosing for the indication of actinic keratoses reads "up to two packets of Zyclara Cream may be applied to the treatment area for each application." Because the number of packets per application vary depending on the indication (up to two packets for actinic keratoses versus one packet for genital warts), DMEPA believes that the language (b) (4) and (b) (4) displayed

on the carton labeling may cause confusion that could lead to wrong dose medication errors and therefore, the language should be removed.

6 REFERENCES

OSE Review #2009-172 dated November 4, 2009; Zyclara Labels and Labeling Review; Miller, Cathy A.

OSE Review #2010-443 dated March 24, 2010; Zyclara Revised Labels and Labeling Review; Miller, Cathy A.

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201153	ORIG-1	GRACEWAY PHARMACEUTICALS LLC	Zyclara (Imiquimod) Cream 3.75%

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
08/19/2010

ZACHARY A OLESZCZUK
08/19/2010

KELLIE A TAYLOR
08/19/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

M E M O R A N D U M

Date: July 2, 2010

From: Amy M. Taylor, MD, MHS, Medical Officer
Pediatric and Maternal Health Staff, Office of New Drugs

Through: Lisa Mathis, MD, OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

To: Susan Walker, MD, Director
Division of Dermatology and Dental Products

Re: Pediatric safety database

Sponsor: Graceway Pharmaceuticals, LLC

Drug: Zyclara™ (imiquimod) 3.75% Cream

Indications: Proposed Indications in the NDA

- For the treatment of external genital and perianal warts/condyloma acuminata in patients 12 years or older

Dosage form and route of administration: Topical cream

Dosing regimen (proposed in the NDA): Apply a thin layer of Zyclara™ Cream (b) (4) once daily for up to 8 weeks.

Document ID Number: NDA 201153

Document Date: February 5, 2010

Consult Question: Has the applicant provided sufficient safety information to support approval of Zyclara 3.75% cream for external

genital warts (EGW) in the [pediatric] population 12 years and above?

Background

The sponsor, Graceway Pharmaceuticals, submitted an NDA for Zyclara™ (imiquimod 3.75%) Cream on February 5, 2010. The proposed indication is for the treatment of external genital and perianal warts/condyloma acuminate in patients 12 years or older. Zyclara (NDA 22-483) was approved for the treatment of actinic keratoses on March 25, 2010. Pediatric studies were waived for this indication because there are too few children with this condition. The Division is planning to convert this current NDA to an efficacy supplement of NDA 22-483.

Pediatric plan

The sponsor submitted a partial waiver for pediatrics studies in children below the age of 12 years. The sponsor's justification for the waiver is that "Necessary studies are impossible or highly impractical because, e.g., the number of patients in that age group is so small or geographically dispersed (21 CFR 214.55(3)(ii)". The sponsor states that external genital warts are primarily associated with a sexually acquired infection with HPV and are unusual in a prepubertal population.

Related product

Aldara® (imiquimod) 5% Cream, marketed by the same sponsor, was originally approved for use in adults to treat external genital and perianal warts/condyloma (NDA 20-723). Subsequently in September 2002, a labeling revision supplement was approved allowing use down to age 12 years. This extension of the age group for the indication was approved without clinical studies in adolescents. The Division informed the sponsor that children down to the age of 12 years would be expected to have the same efficacy as adults, and that there should not be new safety concerns that needed to be addressed with studies.

A pediatric Written Request (WR) was issued for Aldara® December 28, 2001 for the study of the treatment of molluscum contagiosum in pediatric patients aged 2 to 12 years. The sponsor was granted pediatric exclusivity December 13, 2006. The requested studies included two double-blind, vehicle-controlled safety and efficacy studies during which 470 pediatric patients ages 2 to 12 years were exposed to the product for up to 16 weeks. The product failed to demonstrate efficacy in the treatment of molluscum contagiosum and the indication was not approve. In November 2008, in accordance with the BPCA legislative requirement a pediatric-focused safety review was presented to the Pediatric Advisory Committee (PAC).

Zyclara™ clinical trials

The sponsor conducted 3 clinical studies with 2 investigational formulations (3.75% and 2.5%) imiquimod creams.

- One pharmacokinetic study conducted under maximal use with the 3.75% cream
- Two randomized, double-blind, placebo-controlled multi-center Phase 3 clinical studies using 2 active dose groups.

The pharmacokinetic data indicates that the systemic exposure from daily topical application of 3.75% imiquimod cream in adult EGW patients under maximal use

condition is low. The systemic exposure with 3.75% cream is comparable to the currently marketed 5% Aldara® cream dosed a 3 times per week for 16 weeks.

The Phase 3 clinical trials opened enrollment to patients 12 years and older. However, no patients under 15 years were enrolled. Three patients between ages 15 and 17 years were enrolled.

Pediatric safety

The knowledge of the pediatric safety with imiquimod comes from several sources. Aldara® 5% cream was studied in pediatric patients ages 2 to 12 years. A review of AERS data related to imiquimod was presented to the PAC in November 2008. Adult safety data from clinical trials for several indications for Aldara® and Zyclara™ can provide supportive data for a pediatric safety database.

Aldara® pediatric safety data

Aldara® Cream was studied in 702 pediatric patients with molluscum contagiosum with 470 patients exposed to Aldara®. The adverse events seen were similar to those seen in studies with adults, but also included otitis media (5% Aldara vs. 3% vehicle) and conjunctivitis (3% Aldara® vs. 2% vehicle). The most frequently reported adverse events were related to application site reactions. These included erythema (28%), edema (8%), scabbing/crusting (5%), flaking/scaling (5%), erosion (2%) and weeping/exudate (2%). A Pharmacokinetic study in pediatric patients demonstrated that absorption of Aldara® following topical application in pediatric patients was comparable to adults.

Pediatric-focus safety review presented to the PAC

A review by OSE revealed that prescriptions in the pediatric population (ages 0-16 years) accounted for approximately 21% of the total dispensed Aldara® prescriptions. Of the prescriptions dispensed to pediatric patients, 40% were dispensed to patients aged 6-10 years and 38% dispensed to patients 11-16 years. The top diagnoses for the prescriptions were viral warts and molluscum contagiosum.

A review of AERS reports in pediatric patients since marketing approval of Aldara® revealed 12 serious adverse event cases and 1 death involving a 16 year female who committed suicide by gunshot. The most common serious adverse event reported was localized reaction (n 6) including swelling, blisters, burning pain, erosions, ulcerations and abscess. In 3 patients, the localized reaction was associated with an inability to void.

Answer to Division's Question

Has the applicant provided sufficient safety information to support approval of Zyclara™ 3.75% cream for external genital warts (EGW) in the [pediatric] population 12 years and above?

The pediatric safety database for Zyclara™ consist of 3 adolescent patients ages 15 to 17. Typically this would be inadequate to support approval of a product in the pediatric age group. While statute allows extrapolation of efficacy from adults to pediatric patients, safety cannot be extrapolated. In the case of Zyclara™, there is additional safety data for imiquimod which can be used to support the safety of the drug. This includes the safety data derived from clinical studies with Aldara® and the safety review of AERS reports by OSE. Safety cannot be extrapolated from adults to pediatric patients; however, safety information in adults can support a finding of safety in pediatric patients. Additional

support for the safety of Zyclara™ in adolescents is the fact that the product is topical and has a low systemic absorption. The expected adverse events are primarily local reactions and would be expected to be the same for adolescents as adults. Given the additional supportive safety information from experience with use of Aldara® in the pediatric population, one would expect the safety of Zyclara to be similar in adolescents as in adults and additional studies in adolescents are not needed.

Additional Comments

The sponsor has requested a partial waiver of studies required under the Pediatric Research Equity Act (PREA) for pediatric patients below the age of 12 years. The sponsor's justification for the waiver is that necessary studies are impossible or highly impractical. The sponsor states that external genital warts are primarily associated with a sexually acquired infection with HPV and are unusual in a prepubertal population. The waiver request appears reasonable, however it lacks supporting data. Given the new requirements for an internal pediatric review committee to review the data to support the waiver request, it is likely that questions will be raised by the lack of submitted data. (b) (4) It would be helpful for the Sponsor to submit more data to support their waiver request. The only data currently submitted is a chapter from a textbook that incorporates data that is approximately 20 years old (prevalence rates from mid 1980s) and only provides a vague reference to the number of abused patients who may have external genital warts. This will not be sufficient to support a waiver. Examples of data to support the waiver could be more current published medical literature or CDC data on incidence by age group. All requests for waivers must be reviewed by the Pediatric Review Committee (PeRC) prior to action being taken on the NDA.

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

/s/

AMY M TAYLOR
07/23/2010

LISA L MATHIS
08/02/2010

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 201153 BLA#	NDA Supplement #: BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Zyclara Established/Proper Name: imiquimod Dosage Form: Cream Strengths: 3.75%		
Applicant: Graceway Pharmaceuticals, LLC Agent for Applicant (if applicable): N/A		
Date of Application: 2-5-2010 Date of Receipt: 2-8-2010 Date clock started after UN: N/A		
PDUFA Goal Date: 12-8-2010	Action Goal Date (if different): 11-15-2010	
Filing Date: 4-9-2010	Date of Filing Meeting: 3-30-2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed indication(s)/Proposed change(s): Treatment of external genital warts and perianal warts/condyloma acuminate in patients 12 years or older		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html*** ***and refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical

Other:	benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 030432 (EGW), 049480 (AK), 049464 (sBCC)	

Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***		**X**		Email sent to document room to change to Standard review.
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	**X**			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***			**X**	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		**X**		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:			**X**	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	**X**			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).*	

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:				

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5 year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3 year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		**X**		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***			**X**	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	**X**			

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		**X**		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☒ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	Hybrid CTD			
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).		**X**		Waiver Granted
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	**X**			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? ***If yes,*** *date consult sent to the Controlled Substance Staff:*			**X**	
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**X**	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	**X**			
Are all establishments and their registration numbers listed on the form/attached to the form?	**X**			
Patent Information **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?	**X**			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	**X**			FDA 3454
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	**X**			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*		**X**		Sponsor advised to re-submit correct Debarment Certification.

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			**X**	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	**X**			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		**X**		
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	**X**			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***	**X**			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***		**X**		

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***			**X**	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	**X**			
Is the PI submitted in PLR format?	**X**			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***			**X**	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?		**X**		Original NDA to be converted to efficacy supplement. Consult to be requested when revised label is received.
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)		**X**		Original NDA to be converted to efficacy supplement. Consult to be requested when revised label is received.
REMS consulted to OSE/DRISK?			**X**	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?		**X**		Original NDA to be converted to efficacy supplement. Consult to be requested when revised label is received.
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card			

	☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		**X**		

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 1-20-2008 ***If yes, distribute minutes before filing meeting***	**X**			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 11-18-2009 ***If yes, distribute minutes before filing meeting***	**X**			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		**X**		

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 30, 2010

BLA/NDA/Supp #: NDA 201153

PROPRIETARY NAME: Zyclara

ESTABLISHED/PROPER NAME: imiquimod

DOSAGE FORM/STRENGTH: Cream, 3.75%

APPLICANT: Graceway Pharmaceutical, LLC.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

BACKGROUND: Original NDA 201153 Zyclara (imiquimod) Cream, 3.75% was submitted on February 2, 2010 for external genital and perianal warts. This application may be converted to efficacy supplement (S-001) to NDA 022483 Zyclara (imiquimod) Cream, 3.75%.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kelisha Turner	Y
	CPMS/TL:	Margo Owens	N
Cross-Discipline Team Leader (CDTL)	Jill Lindstrom		Y
Clinical	Reviewer:	Milena Lolic	Y
	TL:	Jill Lindstrom	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Edward Bashaw	Y
	TL:		
Biostatistics	Reviewer:	Kathleen Fritsch	Y
	TL:	Mohamed Alosh	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Jerry Wang	Y
	TL:	Barbara Hill	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Shulin Ding	Y
	TL:	Moo Jhong Rhee	N
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review *(for BLAs/BLA supplements)*	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		

Other reviewers		
Other attendees	Stanka Kukich, Barbara Gould, Ramesh Raghavachari	

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: N/A	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: Conducted under original NDA	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

Comments:	

Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**: EA officer not necessary per CMC	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☒ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**: May be converted to an efficacy supplement prior to approval.	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs/BLA supplements only) **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Susan J. Walker, M.D., F.A.A.D **21st Century Review Milestones (see attached)** (optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☐	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201153	ORIG-1	GRACEWAY PHARMACEUTICALS LLC	Zyclara (Imiquimod) Cream 3.75%

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

/s/

KELISHA C TURNER
04/28/2010

MARGO L OWENS
04/28/2010