

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22483Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

Date: 18-MAR-2010
From: Rajiv Agarwal, Ph.D., Review Chemist
Through: Moo-Jhong Rhee, Ph.D., Chief, Branch III/DPA II/ONDQA
To: CMC Review # 1 (23-SEP-09) of NDA 22-483
Subject: Final Recommendation

The previous CMC review indicated the following labeling issue:

The current presentation of the dosage form (Cream) and the strength (3.75%) appear sequentially out of place in carton. They are currently presented above (before) the proprietary and established name. It should appear as follows:

*Zyclara
(imiquimod) Cream
3.75%*

In an amendment dated 16-MAR-2010, the sponsor has committed to modify and implement the requested label presentation style once the current supply of printed material is exhausted (See Attachment-1 for proposed future Fold-Out and Sleeve Carton).

The commitment is deemed acceptable and, therefore, from the CMC perspective, this NDA is now recommended for approval.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22483	ORIG-1	GRACEWAY PHARMACEUTICA LS LLC	IMIQUIMOD 3.75% CREAM

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/s/

RAJIV AGARWAL
03/18/2010

MOO JHONG RHEE
03/18/2010
Chief, Branch III

NDA 22-483

Zyclara (To be decided)

(Imiquimod) Cream

3.75%

For topical use only

Graceway Pharmaceuticals, LLC.

Rajiv Agarwal

Review Chemist

**Office of New Drug Quality Assessment
Division of Pre-Marketing Assessment II
Branch III**

**CMC REVIEW OF NDA 22-483
For the Division of Dermatology and Dental Products (HFD-540)**

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 22-483
2. REVIEW #: 1
3. REVIEW DATE: 21-SEP-2009
4. REVIEWER: Rajiv Agarwal, Ph.D; Ph.D
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	21-DEC-2008
Amendment	01-APR-2009
Amendment	30-APR-2009
Amendment	21-MAY-2009
Amendment	18-JUN-2009
Amendment	16-JUL-2009
Amendment	17-JUL-2009

7. NAME & ADDRESS OF APPLICANT:

Name: Graceway Pharmaceuticals, LLC
Address: 340 Martin Luther King Jr Blvd, Bristol, TN
37620

Representative: Sean Brennan
Telephone: 423-274-5210

8. DRUG PRODUCT NAME/CODE/TYPE:

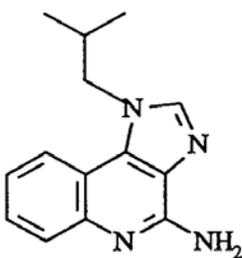
- a) Proprietary Name: Zyclara (Not decided yet)
- Non-Proprietary Name (USAN): Imiquimod
- b) Code Name/# (ONDQA only): none
- c) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 5
 - Submission Priority: S

CMC Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)
10. PHARMACOL. CATEGORY: Actinic keratosis of the face and/or scalp
11. DOSAGE FORM: Cream
12. STRENGTH/POTENCY: 3.75%
13. ROUTE OF ADMINISTRATION: Topical
14. Rx/OTC DISPENSED: Rx OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):
 SPOTS product – Form Completed
 Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Imiquimod (USAN): 1*H*-Imidazo [4,5-*c*] quinolin-4-amine, 1-(2-methylpropyl) and 4-amino-1-isobutyl-1*H*-imidazo [4,5-*c*] quinoline



Molecular Formula: C₁₄H₁₆N₄

Molecular weight: 240.30

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE¹	STATUS²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	1	Adequate	21-SEP-2009	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Cross referenced NDA	20-723	5% strength, Approved in 1997
74-Day letter	22-483	02-MAR-2009

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	ACCEPTABLE	21-SEP-2009	Office of Compliance
Methods Validation	N/A, according to the current ONDQA policy		
Pharm/Tox	Acceptable	3-AUG-2009	Dr. Jianyong Wang
EA	Categorical exclusion granted		

Executive Summary Section

The CMC Review for NDA 22-483

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The final recommendation from the Office of Compliance involving all facilities pertaining to the cGMP inspections of drug substance and drug product manufacturing and testing operations is ACCEPTABLE. However, the established name and dosage form information in carton and container closure labels are not finalized (see the List of Deficiencies, P.52).

Therefore, until the labeling issues are resolved, the NDA is not recommended for APPROVAL from a CMC standpoint.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance:

Imiquimod is a (b) (4) (b) (4) compound manufactured by 3M Sante, Pithiviers, France. It is a (b) (4) (b) (4) odorless compound, with white to off white in color. The solid state was characterized by (b) (4) (b) (4). The drug substance melts at (b) (4) and (b) (4). All lots manufactured were monitored by (b) (4) and the (b) (4) was defined by (b) (4). The drug substance is (b) (4) but is (b) (4) in isostearic acid, (b) (4) in the drug product, to the extent of (b) (4) (b) (4). The solubility data for the drug substance in different lots of isostearic acid were provided in the original NDA. The drug substance does not have DMF but the relevant CMC information was included in the original NDA. *Please refer to CMC review of NDA 20-723 by Mary Ann Jarski for HFD 530 dated 21-JAN-1997 for more information.*

Executive Summary Section

The recommendation from the Office of Compliance pertaining to the manufacturing and testing sites for drug substance is ACCEPTABLE.

(2) Drug Product:

The drug product is a white to faintly yellow topical cream with a uniform appearance, packaged in a form, fill and seal (b) (4) single dose sachet. Each sachet contains 250 mg of imiquimod 3.75% topical cream.

The components of the drug product are the same as those for the approved product Aldara Cream, 5% (imiquimod). The imiquimod cream 3.75% differs only in the reduction of the concentrations of the active ingredient (imiquimod) from 5% to 3.75%, the (b) (4) of isostearic acid from (b) (4) and the concomitant (b) (4) in water content from (b) (4).

The container closure system for imiquimod 3.75% topical cream is the same as that approved for use for the commercial imiquimod 5% topical cream (Aldara®). The container closure system is a form, fill and seal, (b) (4) single dose sachet (packet) consisting of a (b) (4) material which uses aluminum foil (b) (4) (u) (*). The cream (250 mg) is retained in the bottle shaped (b) (4) area of the sachet. The upper corners of the sachet are notched to facilitate opening and the opened area of the bottle shaped (b) (4) is narrower than the base (b) (4).

Information pertaining to the pouching material is presented in DMF (b) (4) (volume 112, page numbers 1 - 93) supplied by (b) (4). A summary of the physiochemical and toxicological tests performed on the (b) (4) material and the intermediate bulk storage containers is provided in the DMF and provided information is deemed adequate.

A 24-month of expiration dating period is requested and it is granted.

The recommendation from the Office of Compliance pertaining to the manufacturing and testing sites for drug product is ACCEPTABLE (Attachment-1).

B. Description of How the Drug Product is Intended to be Used

Daily application of the cream to the skin of the affected area for two week treatment cycles separated by a two week no treatment period.

- An 24-month of expiration dating period is granted.
- The storage condition for the drug product is “Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]”.

Executive Summary Section

C. Basis for Approvability, or Not-approval Recommendation

- This NDA provided adequate information on the raw material controls, manufacturing process, specifications, and container/closure. It also provided sufficient stability data to assure identity, strength, purity and quality of the drug product during the expiration dating period.
- The final recommendation from the Office of Compliance on the compliance to the cGMP involving all facilities pertaining to the drug substance and drug product manufacturing and testing operations is ACCEPTABLE (Attachment-1).
- The only pending issue is that the information on the container/closure labels was not in the recommended format and must be presented as recommended.
- Until the issue is resolved, from a CMC perspective, this NDA is not recommended for approval.

III. Administrative**A. Reviewer's Signature:**

(See appended electronic signature page)

Rajiv Agarwal

B. Endorsement Block:

(See appended electronic signature page)

Moo-Jhong Rhee, Branch Chief, Branch III, ONDQA

C. CC Block: entered electronically in DFS

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22483	ORIG-1	GRACEWAY PHARMACEUTICA LS LLC	IMIQUIMOD 3.75% CREAM
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/s/

RAJIV AGARWAL
09/23/2009

MOO JHONG RHEE
09/23/2009
Chief, Branch III

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division: Division of Dermatology and Dental Products
NDA: 22-483
Applicant: Graceway Pharmaceuticals
Stamp Date: Feb. 8, 2008
PDUFA Date: Oct. 19, 2009
Trademark: To be proposed
Established Name: Imiquimod
Dosage Form: Cream
Route of Administration: Topical
Indication: Actinic keratoses

PAL: Shulin Ding

	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Summary and Critical Issues:

A. Summary

This NDA is a 505(b) (1) submission of Tradename (imiquimod) cream 3.75% for the indication of actinic keratoses. The same indication has been approved for a 5% imiquimod cream (Aldara NDA 20-723), but with a different dosing regimen. Aldara requires a 16-week regimen of twice weekly dosing for a defined 25 cm² treatment area whereas Tradename (imiquimod) cream 3.75% is proposed for a regimen of daily dosing for a shorter duration and over a larger area.

The formulation of the proposed product, Tradename (imiquimod) cream 3.75%, is almost identical to that of Aldara. Both products use the same drug substance supplied by the same supplier (3M Pithiviers, France), and the same inactive ingredients of the same quality. They differ only in the reduction of imiquimod concentration from 5% in Aldara to 3.75%, the (b) (4) of isostearic acid (b) (4) from (b) (4) in Aldara to (b) (4) and the concomitant (b) (4) in water content from (b) (4) in Aldara to (b) (4)

The proposed product has also the same drug product manufacturing/packaging process and container/closure system (250 mg fill size, (b) (4) (b) (4) (b) (4) single dose sachet) as those of Aldara. The same DMF (b) (4) is referenced for the (b) (4)

The proposed to-be-marketed formulation is the same formulation used in the pivotal clinical trials and registration stability studies. The formulation contains the following excipients: isostearic acid, benzyl alcohol, NF; cetyl alcohol, NF; stearyl alcohol, NF; white petrolatum, USP; polysorbate 60, NF; sorbitan monostearate, NF; glycerin, USP; xanthan gum, NF; methyl paraben, NF; propyl paraben, NF; and purified water, USP. All excipients are compendial except isostearic acid.

The proposed commercial manufacturing scale is (b) (4). The designated commercial site, 3M Health Care Limited (Derbyshire, UK), is also the manufacturing site of clinical/stability batches of this NDA and the production site of Aldara. The commercial manufacturing process consists of the following steps (b) (4)

Stability data provided in the initial submission to support an expiry period of 24 months at (b) (4) 77°F (b) (4) 25°C include 3-9 months of long term (25°C/60% RH), and 3-6 months of accelerated temperature (40°C/75% RH) data from four commercial scale batches. There are no special stability data (such as refrigeration, temperature cycling, freeze/thaw, etc.) provided in the NDA to support storage/handling/shipping of the product.

B. Critical issues for review

Dosage Form Nomenclature

- The applicant proposes cream as the dosage form. It is noted that the viscosity of the product declines substantially upon storage. (b) (4)

To ensure that the product at the lower limit of the viscosity specification will still meet CDER's current thinking about cream, 6 month 40°C stability samples should be submitted for dosage form evaluation along with rheograms (viscosity versus shear rate and shear stress versus shear rate). Room temperature samples should also be submitted with their rheograms for comparison.

Drug Product

Related Substances

- A new impurity, (b) (4) has been detected in (b) (4). The identity of this new impurity has been confirmed. The structure of this new impurity is such that it may have a mutagenicity potential. Its level in the 40°C, 6 month sample was found to be (b) (4). This new impurity has not been detected in the 25°C stability samples up to 6 months.

Since information available for this new impurity is very little and no experience can be drawn from Aldara, CMC review should attend to this issue as early as possible so that information request items can be timely identified and sent to the applicant. It will require a critical review to decide how to deal with this newly discovered impurity.

Related Substances Specification

- The applicant proposes to use the same specification approved for Aldara for this product. Aldara's related substances specification was approved more than 10 years ago, and is not structured in line with ICH Q3B guideline. It does not include elements such as individual unspecified and total degradants. This

outdated specification is inadequate to assure product purity, especially in light of the discovery of a new impurity.

Stability

- The applicant proposes a 24 month expiration date period at (b) (4) 25°C for the drug product. However, (b) (4) stability data are not provided in the NDA. The applicant does not include (b) (4) in the protocols of the registration and post-approval stability studies.

C. Comments for 74-Day Letter:

- Submit 6 month 40°C samples (six units from each registration stability lot) to the NDA with rheograms (viscosity versus shear rate and shear stress versus shear rate) to assist the assessment of dosage form. Submit 25°C stability samples (six units from each registration stability lot) with rheograms for comparison.
- Provide updated drug product stability data including quantitative information of the new impurity (b) (4) each specified identified degradant, each specified unidentified degradant, individual unspecified related substance, total unspecified related substances, and total related substances for the four registration stability lots of the proposed product.
- Provide quantitative information for the new impurity (b) (4) in the clinical and toxicology test materials including the 5% imiquimod cream.

D. Comments/Recommendation:

The application is fileable from the CMC perspective.

The major review issues of this NDA include dosage form, impurities, drug product specification, and drug product stability. Drug substance manufacturing site is located in France. Drug product manufacturing site is located in the United Kingdom. GMP inspection requests have been submitted.

Shulin Ding
Pharmaceutical Assessment Lead

Moo-Jhong Rhee
Chief, Branch III

Filing Checklists

A. Administrative Checklists

YES	NO		Comments
x		On its face, is the section organized adequately?	
x		Is the section indexed and paginated adequately?	
x		On its face, is the section legible?	
x		Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	
x		Has an environmental assessment report or categorical exclusion been provided?	

B. Technical Checklists

1. Drug Substance: Imiquimod

	x	Does the section contain synthetic scheme with in-process parameters?	Reference to NDA 20-723
	x	Does the section contain structural elucidation data?	Reference to NDA 20-723
	x	Does the section contain specifications?	Reference to NDA 20-723
	x	Does the section contain information on impurities?	Reference to NDA 20-723
	x	Does the section contain validation data for analytical methods?	Reference to NDA 20-723
	x	Does the section contain container and closure information?	Reference to NDA 20-723
	x	Does the section contain stability data?	Reference to NDA 20-723

2. Drug Product

x		Does the section contain manufacturing process with in-process controls?	
x		Does the section contain quality controls of excipients?	
x		Does the section contain information on composition?	
x		Does the section contain specifications?	
x		Does the section contain information on degradation products?	
x		Does the section contain validation data for analytical methods?	
x		Does the section contain information on container and closure systems?	
x		Does the section contain stability data with a proposed expiration date?	
x		Does the section contain information on labels of container and cartons?	
x		Does the section contain tradename and established name?	Trade name to be proposed

C. Review Issues

x		Has all information requested during the IND phases, and at the	
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		pre-NDA meetings been included?	
	x	Is a team review recommended?	
x		Are DMFs adequately referenced?	

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/s/

Shulin Ding
2/2/2009 12:24:54 PM
CHEMIST

Moo-Jhong Rhee
2/2/2009 03:47:57 PM
CHEMIST
Chief, Branch III