CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201153Orig1s000

CHEMISTRY REVIEW(S)

NDA 201-153

Zyclara (Imiquimod) Cream 3.75%

Graceway Pharmaceuticals, LLC.

CMC Review for Division of Dermatology and Dental Products

Shulin Ding, Ph.D.

Branch IV, Division of New Drug Quality Assessment II

Office of New Drug Quality Assessment

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CMC Review Data Sheet

1. NDA 201-153

2. REVIEW #: 1

3. REVIEW DATE: Sep. 16, 2010

4. REVIEWER: Shulin Ding, Ph.D

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	Feb. 5, 2010
Amendment[1]	June 8, 2010
Amendment[2]	Aug. 26, 2010

[1]Provides for a revised labeling.
[2]Provides for a revised carton label.

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
Non-Proprietary Name (USAN): Imiquimod
b) Code Name/# (ONDQA only): none
c) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 6
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: not known

CMC Review Data Sheet

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: 3.75%

13. ROUTE OF ADMINISTRATION: Topical

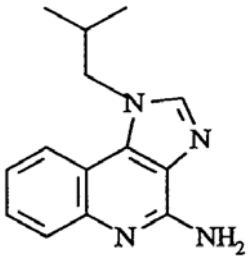
14. Rx/OTC DISPENSED: __√__Rx ___OTC

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: $C_{14}H_{16}N_4$
Molecular weight: 240.30

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	3	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	22-483	Approved on March 25, 2010

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	ACCEPTABLE	May 28, 2010	Office of Compliance
EA	Categorical exclusion granted	Aug.6, 2010	Shulin Ding

The CMC Review for NDA 201-153

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. All facilities involved are in compliance with cGMP, and labels/labeling have adequate information required. Therefore, from a CMC perspective, this NDA is recommended for **"Approval".**

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)

The proposed product is the approved Zyclara (imiquimod) cream, 3.75%. The applicant references to NDA 22-483 for CMC information of the drug substance and the drug product, and states that all information contained in the CMC section of this NDA, with the exception of stability data at the 18 month time point for batch JB071A, was previously submitted to NDA 22-483 and its amendments. There are no changes in the chemistry, manufacturing, and controls of Zyclara (imiquimod) cream 3.75% since the approval of NDA 22-483 on March 25, 2010.

The approved Zyclara (imiquimod) cream, 3.75% is a white to faintly yellow topical cream packaged in a form, fill and seal (b) (4) single dose sachet. Each sachet contains 250 mg of imiquimod cream. The product has been granted with an expiration dating period of 24-month through the approval of NDA 22-483 when stored at 25ºC with excursion permitted to 15º to 30ºC. No extension of the expiration dating period or a change in storage condition is granted through this NDA.

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

Once daily to the external genital/perianal warts until total clearance or up to 8 weeks.

C. Basis for Approvability, or Not-approval Recommendation

The NDA provided adequate information on the drug substance, formulation, the raw material controls, manufacturing process, specifications, and container/closures. It also provided sufficient stability data to assure the strength, purity, and quality of the drug product throughout its expiration dating period. On May 28, 2010, the Office of Compliance has issued an "Acceptable" overall recommendation for all the facilities involved (Attachment 1). Labels/labeling have required information.

III. Administrative

A. Reviewer's Signature: in DARRTS

B. Endorsement Block:n in DARRTS

C. CC Block: in DARRTS

6 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

SHULIN DING
09/29/2010

MOO JHONG RHEE
09/29/2010
Chief, Branch IV

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division:	Division of Dermatology and Dental Products
NDA:	201153
Applicant:	Graceway Pharmaceuticals
Stamp Date:	Feb. 8, 2010
PDUFA Date	Dec. 8, 2010
Trademark:	Zyclara™
Established Name:	Imiquimod
Dosage Form:	Cream
Route of Administration:	Topical
Indication:	Treatment of external genital and perianal warts/condyloma acuminate in patients 12 years or older
PAL:	Shulin Ding

	YES	NO
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☐	☒

Summary and Critical Issues:

A. Summary

This NDA is a 505(b) (1) submission of Zyclara™ (imiquimod) cream 3.75% for the indication of treatment of external genital and perianal warts/condyloma acuminate in patients 12 years or older. The same product has been approved for actinic keratoses (NDA 22-483, approved on 3/25/2010). This NDA is being planned to be converted to an efficacy supplement of NDA 22-483.

Per the applicant's statement in the introductory paragraph of Quality Overall Summary (section 2.3), all information contained in the CMC section of this NDA, with the exception of stability data at the 18 month time point for batch JB071A, was previously submitted to NDA 22-483 and its amendments. There are no changes in the chemistry, manufacturing, and controls of Zyclara (imiquimod) cream 3.75% since the approval of NDA 22-483 on March 25, 2010.

The expiration dating period granted through the approval of NDA 22-483 for Zyclara (imiquimod) cream 3.75% is 24 month when stored at 25ºC with excursion permitted to 15ºC to 30ºC. In this NDA, the applicant requests the same expiration dating period (i.e. 24 months) and storage condition.

B. Critical issues for review

None.

C. Comments for 74-Day Letter:

None

D. Comments/Recommendation:

The application is fileable from the CMC perspective.

Drug substance manufacturing site is located in (b) (4) Drug product manufacturing site is located in (b) (4) GMP inspection requests have not been made since this NDA is to be converted to and reviewed as an efficacy supplement, and there are no changes in manufacturing sites and process.

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?	

C. Review Issues

x		Has all information requested during the IND phases, and at the pre-NDA meetings been included?	

	x	Is a team review recommended?	
x		Are DMFs adequately referenced?	

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/

SHULIN DING
04/05/2010

MOO JHONG RHEE
04/06/2010
Chief, Branch III