

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

22483Orig1s000

Trade Name: Zyclara, 3.75%

Generic Name: Imiquimod

Sponsor: Graceway Pharmaceuticals, LLC

Approval Date: March 25, 2010

Indications: For the topical treatment of clinically typical, visible or palpable actinic keratoses (AK) of the full face or balding scalp in immunocompetent adults.

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APPROVAL LETTER



NDA 022483

NDA APPROVAL

Graceway Pharmaceuticals, LLC
Attention: Sean Brennan, Ph.D.
Vice President, Regulatory Affairs
340 Martin Luther King Jr. Blvd.
Bristol, TN 37620

Dear Dr. Brennan:

Please refer to your new drug application (NDA) dated December 19, 2008, received December 19, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyclara (imiquimod) Cream, 3.75%.

We acknowledge receipt of your submissions dated October 22, November 6, and December 16, 2009; February 12, 23, 25, and 26, March 12, 15, 17, 18, and 22(2) 2010.

The January 29, 2010, submission constituted a complete response to our October 16, 2009, action letter.

This new drug application provides for the use of Zyclara (imiquimod) Cream, 3.75% for actinic keratosis of the face and/or scalp.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions listed below.

1. In the Full Prescribing Information: Contents section, the subheading 17.7 FDA-Approved Patient Labeling was deleted (§201.57(c)(18)).
2. Addition of Header - Section 17: "PATIENT COUNSELING INFORMATION".
3. "PATIENT INFORMATION" was changed to "FDA-Approved Patient Labeling" (§201.57(c)(18)).
4. Under FDA-Approved Patient Labeling, the following language has been deleted
(b) (4) and the phone number moved to be consistent with the information presented in the package insert.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert, text for the patient package insert). For administrative purposes, please designate this submission, “**SPL for approved NDA 022483.**”

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the submitted carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 022483.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable because there are too few children with the disease/condition to study.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of treatment related change in cardiac rate and rhythm.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of treatment related change in cardiac rate and rhythm.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1616-1 Conduct a randomized crossover clinical trial (Zyclara Cream, 3.75% vs. vehicle) in patients with actinic keratosis to detect treatment-related change in atrial ectopy.

The timetable you submitted on March 17, 2010, states that you will conduct this trial according to the following timetable:

Final Protocol Submission:	September 2010
Trial Completion Date:	September 2011
Final Report Submission:	March 2012

Submit the protocol to your IND, with a cross-reference letter to this NDA 022483. Submit all final reports to your NDA 022483. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to

submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package inserts to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package inserts, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

Please submit one market package of the drug product when it is available.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kelisha C. Turner, Regulatory Project Manager, at (301) 796-0766.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

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

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

/s/

SUSAN J WALKER
03/25/2010