

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22483Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	March 22 nd , 2010
From	Susan J. Walker, M.D., F.A.A.D Director, Division of Dermatology and Dental Products
Subject	Division Director Summary Review
NDA #	22-483
Applicant Name	Graceway Pharmaceuticals
Date of Submission	December 19 th , 2008; January 29 th , 2010
PDUFA Goal Date	March 29 th , 2010
Established (USAN) Name	Imiquimod
Dosage Forms / Strength	Cream 3.75%
Proposed Indication(s)	Actinic keratoses
Action	<i>Approval</i>

Material Reviewed/Consulted	Names of discipline reviewers (if applicable)
OND Action Package, including:	
Medical Officer Review	Milena Lolic (Jill Lindstrom – TL)
CDTL Review	Jill Lindstrom
Statistical Review	Kathleen Fritsch (Mohamed Alesh – TL)
Pharmacology Toxicology Review	Jerry (Jianyong) Wang (Barbara Hill – TL)
CMC Review/OBP Review	Rajiv Agarwal (Moo Jhong Rhee – Chief)
Clinical Pharmacology Review	Edward Bashaw
DDMAC	Andy Haffer; Shefali Doshi
DSI	Roy Blay (Tejashri Purohit-Sheth– Chief); A. Dasgupta
OSE/DMEPA	Cathy Miller (Kellie Taylor – TL)
OSE/DRISK	Jessica Diaz (LaShawn Griffiths – TL)
Other	OSE Div. of Epi. –P. Greene, L.Governale – TL) OSE/DPV I – Namita Kothary (Ida-Lina Diak – TL) DCRP – Shari Targum (N. Stockbridge – Director) DCRP(QT) – C. Garnett; S. Balakrishnan

OND=Office of New Drugs
 DDMAC=Division of Drug Marketing, Advertising and Communication
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DSI=Division of Scientific Investigations
 DDRE= Division of Drug Risk Evaluation
 DRISK=Division of Risk Management
 CDTL=Cross-Discipline Team Leader

Signatory Authority Review

1. Introduction

ZYCLARA (imiquimod) Cream, 3.75%, is a topical drug product for which the applicant seeks approval under Section 505 (b) (1) of the Federal Food Drug and Cosmetic Act for the topical treatment of clinically typical actinic keratoses (AK) on the face or scalp in immunocompetent adults. The original application was submitted on January 30th, 2009 and received a Complete Response on October 16th, 2009 with deficiencies in clinical information. The applicant has adequately addressed these issues. This memo will present/summarize the findings of the discipline reviewers and provide the basis for approval for this product.

2. Background

Imiquimod, an imidazoquinolinamine, is thought to be a toll-like receptor agonist that acts on TLR7 and induces the production of various cytokines including interferon alpha, interleukin-12, and tumor necrosis factor-alpha. Imiquimod is currently marketed in the US as a 5% cream under the tradename ALDARA. ALDARA received approval for the treatment of external genital warts (EGW) in 1997, and subsequently received approvals for the treatment of AKs in March 2004 and superficial basal cell carcinoma (sBCC) in July 2004.

The approved dosage regimen for ALDARA for the treatment of actinic keratoses is application of one packet to a treatment field of 25cm² on the face or balding scalp twice weekly for sixteen weeks. This application proposes approval for a 3.75% cream (ZYCLARA) for the treatment of a larger field (entire face or balding scalp) using a dosage regimen consisting of application of up to two packets to the treatment area once daily for two 2-week treatment cycles separated by a 2-week rest period.

Actinic keratoses are dysplastic lesions of the epidermis that are thought to be induced by chronic ultraviolet radiation exposure. Clinically-typical AK lesions are yellow-to-red papules with a rough surface which may be more easily palpated than visualized. They may be tender or asymptomatic. Although AKs can progress to squamous cell carcinoma, the rate of malignant transformation is low. AKs may also resolve spontaneously.

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Carton/Container labeling issues have been resolved with submission of March 22nd.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The applicant submitted data from two pivotal trials, Study GW01-0702 and Study GW01-0704 (hereafter 702 and 704, respectively), to establish the effectiveness of their product applied daily for two 2-week treatment cycles separated by a 2-week rest period in the treatment of actinic keratoses. Both trials were multi-center, prospective, randomized, double-blind, parallel-group studies with three arms: 2.5% imiquimod, 3.75% imiquimod and vehicle. The population enrolled were subjects 18 years of age and older with 5 to 20 non-hyperkeratotic, non-hypertrophic, AKs involving an area greater than 25cm² on either the face or balding scalp. In addition to the two pivotal trials, the applicant also submitted data from two supportive trials (703 and 705) which evaluated the same dosage strengths using two 3-week treatment cycles separated by a 3-week rest period.

The primary efficacy measure was AK lesion counts. The primary efficacy evaluation was 8 weeks after completion of treatment, which was week 14 in the pivotal trials and week 17 in the supportive trials due to the differing regimens. The primary efficacy endpoint was the complete clearance rate, defined as the proportion of subjects with no clinically visible or palpable AK lesions in the treatment area. The efficacy results, from Dr. Kathleen Fritsch's review, are presented in the table below.

Complete Clearance Rates 8 Weeks Post-Treatment (ITT)

	ZYCLARA 2.5% cream	ZYCLARA 3.75% cream	Vehicle cream
Study 702	23.5% (19/81)	25.9% (21/81)	2.5% (2/80)
Study 704	38.0% (30/79)	45.6% (36/79)	10.1% (8/79)
Study 703	23.2% (12/82)	32.5% (26/80)	5.1% (4/78)
Study 705	26.8% (22/82)	35.4% (29/82)	5.8% (29/82)

Both concentrations at both dosing regimens were superior to vehicle in the proportion of subjects that achieved complete clearance of their AKs. The complete clearance rate was slightly higher for the 3.75% than the 2.5% strength. The data from the pivotal and supportive trials, detailed in the reviews by Drs. Lolic and Fritsch, support the determination of efficacy.

8. Safety

The safety database is derived from five studies (two pivotal phase 3 studies, two supportive phase 3 studies, and a PK study), and includes 665 subjects exposed to imiquimod, 341 of whom received 3.75% cream (160 for 2-week cycles and 181 for 3-week cycles) and 324 of whom received 2.5% cream (160 for 2-week cycles and 164 for 3-week cycles). The safety database is adequate.

There were no deaths in the development program. There were 33 serious adverse events in 25 subjects, 12 in the 3.75% group, 9 in the 2.5% group, and 4 in the placebo group. Two SAEs, diarrhea and pancytopenia, were considered by the investigator to be probably related to study drug treatment. In her review, Dr. Lolic found the pancytopenia case to be confounded by the subject's prior medical history and concomitant medication use (colchicine), but could not exclude an association with study drug.

The most common AEs were headache, local site reactions, fatigue and nausea. Local site reactions were more frequent and more severe in the 3.75% group vs. the 2.5% group, and in the 3-week cycle group vs. the 2-week cycle group. Collection of adverse event data and assessment of local tolerance did not reveal unexpected safety signals.

During the first cycle the applicant was advised that there was an informational need regarding the impact of their product on cardiac repolarization and heart rate. The application did not contain EKG evaluation in the clinical studies submitted support of this product and a TQT study was not conducted to assess the impact of the product on cardiac repolarization.

In the resubmission, the applicant provided ECG data which was obtained during the development of Aldara (imiquimod) 5% cream but not included with the original submission or provided during the first review cycle of NDA 22-483. Consultative review was obtained from the QT Interdisciplinary Review Team regarding the adequacy of this data to address the impact of imiquimod on QT interval. The QT-IRT found the submitted data, "are sufficient," and that "further study is [not] needed to characterize imiquimod's effect on QT." The

applicant has agreed to conduct a randomized crossover study (Zyclara Cream, 3.75% vs. vehicle) in patients with actinic keratosis to detect treatment-related change in atrial ectopy

9. Advisory Committee Meeting

The application was not presented at an Advisory Committee meeting. Imiquimod is not a new molecular entity; a 5% concentration of the drug product is approved for a similar indication. Review of the application did not identify novel issues which would merit Advisory Committee input.

10. Pediatrics

Actinic keratoses are caused by chronic ultraviolet radiation exposure and occur almost exclusively in adults. Actinic keratoses are seen in children with xeroderma pigmentosa, a condition caused by defective DNA repair mechanisms, but this genodermatosis is rare. The applicant requested a waiver for all pediatric age groups on the grounds that pediatric studies would be impossible or highly impracticable because there are too few children with the disease/condition to study. The application was presented to the Pediatric Review Committee (PeRC) on June 24, 2009; PeRC agreed with the Division's recommendation to grant a complete pediatric waiver.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

Final product labeling is attached to the approval letter.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – The product will be approved.
- Risk Benefit Assessment – In my opinion, the benefits from therapy with this product outweigh the risks.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies - None
- Recommendation for other Postmarketing Requirements and Commitments – The applicant has agreed to conduct a randomized crossover study (Zyclara Cream, 3.75% vs. vehicle) in patients with actinic keratoses to detect treatment-related change in atrial ectopy.

Susan J. Walker, MD, FAAD
Director
Division of Dermatology and Dental Products

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
03/22/2010