

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22483Orig1s000

OTHER REVIEW(S)



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: March 23, 2010

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

Through: Kellie Taylor, PharmD, Associate Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Cathy A. Miller, BSN, MPH, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Zyclara (Imiquimod) Cream
3.75%

Application Type/Number: NDA 022483

Applicant: Graceway Pharmaceuticals,

OSE RCM #: 2010-443

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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 revised container labels, carton and insert labeling for areas that could lead to medication errors.

1.1 REGULATORY HISTORY

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.

2 METHODS AND RESULTS

2.1 LABELS AND LABELING

DMEPA used Failure Mode and Effects Analysis (FMEA)¹ in our evaluation of carton labeling and insert labeling submitted on February 23, 2010 (see Appendices A and B). Although the Applicant's resubmission included the container label for the single-use sachet, no changes were made to the label since our previous review and therefore, DMEPA has no additional comments.

3 RECOMMENDATIONS

Our evaluation noted areas where information on the carton labeling can be improved to minimize medication errors. Section 3.1 *Comments to the Division*, contains our recommendations for the insert labeling. Section 3.2 *Comments to the Applicant*, contains our recommendations for the carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Janet Anderson, OSE Project Manager, at 301-796-0675.

3.1 COMMENTS TO THE DIVISION

DMEPA has made recommendations in Section 3.2 Comments to the Applicant regarding the language (b) (4) on the carton labeling. The words (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". Because we are recommending that this language be removed from carton labeling, we are also requesting that the language be omitted from the insert labeling as follows:

A. Dosage and Administration Section

1. Remove the words (b) (4) from the last paragraph of Section 2.1 and replace with either 'boxes' or 'cartons'.

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

B. How Supplied/Storage and Handling

2. Remove the words (b) (4) that appears in Section 16 and replace with either 'box' or 'carton'.

3.2 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 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".

4 REFERENCES

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

2 pages 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/

CATHY A MILLER
03/23/2010

KELLIE A TAYLOR
03/24/2010

DENISE P TOYER on behalf of CAROL A HOLQUIST
03/24/2010

Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for each PMR/PMC in the Action Package.

PMR/PMC Title: Conduct a randomized crossover study (Zyclara 3.75% vs. vehicle) in patients with AK to detect treatment-related change in atrial ectopy.

PMR/PMC Schedule Milestones:

Protocol Submission Date:	<u>09/30/2010</u>
Study Initiation Date:	<u>MM/DD/YYYY</u>
Study Completion Date:	<u>09/30/2011</u>
Final Study Report Submission Date:	<u>03/31/2012</u>
Other: _____	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

On 10/16/2009 CR letter was issued for NDA 22-483 with request to "conduct the TQT study with Holter monitoring to demonstrate the impact of Zyclara on cardiac repolarization and heart rate". Following dispute resolution, applicant provided additional safety data in their NDA resubmission including prior clinical experience with imiquimod 5% cream and one PK study (with oral imiquimod) with QT-interval measurements. While QT data are reassuring, prior clinical experience data does not fully alleviate the concern about heart rare and rhythm due to the very limited electrocardiographic tracing during the development program.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

Typically applied imiquimod 3.75% cream produces low, but detectible systemic levels. Three cases of symptomatic arrhythmias with positive rechallenge were reported in AERS data- base of imiquimod 5% cream arising the question of possible imiquimod related arrhythmias.

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

Zyclara 3.73% cream is developed for the treatment of AK keratosis (non-life threatening disease) that is occurring in older population. The affected population is known to have higher risk for developing cardiovascular conditions including heart rate and rhythm abnormalities. Pro-arrhythmic drug may increase that risk. Furthermore, the physiological response to heart rate and rhythm change is frequently diminished in elderly population (due to aging, concomitant medications and conditions) causing more severe consequences.

- **If the PMR is a FDAAA safety study/clinical trial, does it:**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

N/A

4. If not required by regulation, characterize the review issue leading to this PMC

N/A

5. What type of study or clinical trial is required or agreed upon (describe)?

Sponsor proposes to conduct a two-way randomized, cross over trial in 50 subjects with actinic keratosis using standard 24-hour Holter monitoring to detect treatment-related change in atrial ectopic frequency.

Required

- Pharmacoepidemiologic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)
cardiac rate and rhythm changes

- Subpopulation (list type)

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study
(provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other
Clinical trial designed to detect change in atrial ectopy

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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/s/

KELISHA C TURNER
03/18/2010

TATIANA OUSSOVA
03/18/2010



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: March 3, 2010

To: Susan J. Walker, MD, Division Director
Division of Dermatological and Dental Products

Through: Claudia Karwoski, PharmD, Division Director
Division of Risk Management (DRISK)
LaShawn Griffiths, RN, MSHS-PH, BSN, Acting Team
Leader Patient Labeling Reviewer
Division of Risk Management

From: Jessica M. Diaz, RN, BSN
Patient Product Information Reviewer
Division of Risk Management

Subject: DRISK Review #2 of Patient Labeling (Patient Package
Insert)

Drug Name(s): ZYCLARA (imiquimod) Cream 3.75%

Application
Type/Number: NDA 22-483

Applicant/sponsor: Graceway Pharmaceuticals, LLC

OSE RCM #: 2009-174

1 INTRODUCTION

This memo is written in response to a request by the Division of Dermatological 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 resubmitted on February 23, 2010.

On October 13, 2009 DRISK completed their original review of the Zyclara cream Prescribing Information (PI) and PPI submitted on April 14, 2009. On October 16, 2009, DDDP sent a Complete Response to Graceway Pharmaceuticals, LLC regarding a deficiency in electrocardiographic studies, specifically QT studies. This memo provides information regarding the review of the PPI.

Please let us know if DDDP would like a meeting to discuss this review.

2 MATERIAL REVIEWED

- DRISK review of the ZYCLARA (imiquimod) cream dated October 13, 2009.
- Draft ZYCLARA (imiquimod) cream Prescribing Information (PI) submitted February 23, 2010 and revised by the Review Division throughout the current review cycle.
- Draft ZYCLARA (imiquimod) cream Patient Package Insert (PPI) submitted on February 23, 2010.

3 RESULTS OF REVIEW

In our review of the PPI (Appendix A: PPI Marked Copy, Appendix B: PPI Clean Copy), we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information

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 has been withheld in full immediately following this page as B4 CCI/TS

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/s/

JESSICA M DIAZ
03/03/2010

CLAUDIA B KARWOSKI
03/03/2010
concur



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: March 1, 2010

From: Christine Garnett, Pharm.D.
Suchitra Balakrishnan, M.D., Ph.D.
CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Kelisha Turner
Regulatory Project Manager
Division of Dermatology and Dental Products

Subject: QT-IRT Consult to NDA 022483

This memo responds to your consult to us dated February 5, 2010 regarding Class 1 Resubmission for Zyclara (imiquimod) Cream, sponsored by Graceway Pharmaceuticals, LLC. The QT-IRT received and reviewed the following materials:

- Your consult
- Response Summary
- Study report for R-837-009
- ECG tracings for R-837-009
- Assessment of available data on heart rate and potential symptomatic tachyarrhythmia (attachment 16 & 17, SDN 022 to NDA 022483 dated January 29, 2010)

QT-IRT Responses to Questions Posed by DDDP

1. Do the results of the study R-837-009 provide sufficient information about imiquimod impact on heart rate, cardiac rhythm and QT interval?

Yes, the data are sufficient. There does not appear to be significant effects of imiquimod on the QT interval. Specifically, no subject had an absolute QTcF over 450 ms post-treatment at exposures over 100-fold compared to the topical preparation. The only irregular rhythm seen was sinus arrhythmia in two subjects which is a normal variant. No clinically significant ECG

changes were reported for any subject. Increases in HR were noted in both R837-009 and R837-019 following single oral doses of imiquimod, which give >100-fold greater imiquimod exposures than imiquimod cream 3.75%. This does not seem to be clinically significant because most HR values are around 70 bpm or less which is reassuring, and there were no tachycardic or bradycardic outliers.

It is possible that effects of imiquimod on endogenous interferons with chronic use produce increases in HR and potential arrhythmias in a vulnerable population that is not dose-dependent. However, this is best addressed by review of symptomatic arrhythmia incidence in placebo-controlled clinical trial data.

2. Does the single oral dose study R-837-009 sufficiently address the imiquimod impact on heart rate, cardiac rhythm and QT interval given that imiquimod as labeled is intended for multiple topical dosing?

Yes, the data are reassuring that there is not a direct effect on QT, heart rate, and rhythm. Single oral doses (100 mg to 300 mg) give supratherapeutic imiquimod concentrations for evaluation of QT, heart rate and cardiac rhythm. Following administration of 3.75% imiquimod cream applied to the face and/or scalp 7 times per week for 3 weeks, steady state mean C_{max} and AUC values are 0.323 ± 0.159 ng/ml and 5.97 ± 3.09 ng.h/ml (study GW01-0706). The imiquimod exposures in study R-837-009 are >100-fold the topical exposures. For example, mean C_{max} and AUC values for the 300-mg oral dose are 528 ng/ml and 5072 ng.h/ml.

To address chronic use, a review of the clinical database showed the incidence of cardiac AEs related to rate and rhythm disturbances was similar to placebo and possibly represents the background rate of these events.

3. Following the review of the study R-837-009, what is your recommendation regarding the need for any further studies related to imiquimod's impact on heart rate, cardiac rhythm and QT interval?

We do not think a further study is needed to characterize imiquimod's effect on QT. We defer to Dr. Targum's opinion and review of draft protocol (b) (4) - (b) (4) for further assessments related to imiquimod's effect on heart rate and rhythm.

BACKGROUND

On October 16, 2009 the Division issued a Complete Response letter for Zyclara (imiquimod) Cream, with a description of the information required to be included in a complete resubmission. Following receipt of the Complete Response letter, additional discussions with the sponsor were held including a Type A Meeting held on November 17, 2009, and the submission of a Formal Dispute Resolution Request on December 16, 2009. In response to Dispute Resolution, a Dispute Appeal – Response letter was issued on January 15, 2010 by Julie Beitz MD, Director, ODE-3. The Response letter included a revised description of the information to be included in complete response to the October 16, 2009 letter, and clarification that this response would be considered a Class 1 resubmission.

Study R-837-009

Study Design

The study was a single-blind, placebo-controlled, single oral escalating dose safety trial in 40 healthy male volunteers. A single dose of R-837 or placebo was administered following an overnight fast. Four dose levels were administered: 100 mg, 200 mg, 250 mg and 300 mg.

Treatment Arms

Total Dose (R-837)	1	2	Capsule No.	
			3	4
100 mg:	100 ^a	PC ^b	PC	PC
200 mg:	100	100	PC	PC
250 mg:	250	PC	PC	PC
300 mg:	100	100	100	PC
Placebo:	PC	PC	PC	PC

^aAmount (mg) of R-837 contained in each capsule.

^bPlacebo capsule (lactose filled).

A 12-lead ECG and interpretation was performed predose and 2, 4, 8, and 24 hours after drug administration. Blood samples for PK assessments were obtained predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours after drug administration.

Study Results (from original study report)

A summary of PK parameters by dose level is presented in sponsor's Table 19. Peak concentrations occurred between 2–4 hours after dosing in all but one subject, No. 63, for whom the observed Tmax was 6 hours.

TABLE 19
 MEAN ± SD PHARMACOKINETIC PARAMETERS FOR R-837 FOLLOWING ADMINISTRATION
 OF SINGLE ORAL DOSES OF 100, 200, 250 OR 300 MG R-837 TO HEALTHY SUBJECTS

Parameter ^a	100 mg ^b		200 mg ^b		250 mg ^b		300 mg ^c	
AUC _{0-∞} (ng x hr/mL)	573	± 301	1728	± 1183	2059	± 1405	5072	± 2294
C _{max} (ng/mL)	120	± 60	281	± 138	359	± 230	528	± 128
T _{max} (hr)	3.2	± 0.8	3.0	± 1.1	2.7	± 0.5	3.8	± 0.8
CL (L/hr)	222	± 115	173	± 113	221	± 193	74	± 39
CL (L/hr/kg)	3	± 1	2	± 1	3	± 3	1	± 1
CL (mL/min)	3703	± 1927	2886	± 1885	3678	± 3225	1227	± 656
CL (mL/min/kg)	49	± 25	36	± 22	48	± 44	16	± 8
V _{dss} (L)	846	± 307	752	± 367	1300	± 1034	473	± 182
V _{d(ss)} (L/kg)	11	± 4	9	± 4	17	± 13	6	± 2
V _{d(area)} (L)	764	± 249	814	± 554	1372	± 1245	414	± 150
V _{d(areg)} (L/kg)	10	± 3	10	± 7	18	± 17	6	± 2
K _a (hr ⁻¹)	0.927	± 0.268 ^d	1.150	± 0.470 ^e	1.061	± 0.418 ^d	0.768	± 0.295
K _{el} (hr ⁻¹)	0.281	± 0.077	0.220	± 0.087	0.206	± 0.100	0.174	± 0.051
t _{1/2el} (hr)	2.7	± 0.8	3.6	± 1.4	4.4	± 2.7	4.4	± 1.6

^a The term F (fraction of dose absorbed) was assumed to be one for CL and V_d calculations

^b N=6

^c N=12

^d N=4

^e N=5

Notebook References: 86333-78, 80, 82, 110; 88459-5, 6

There were no clinically significant changes in ECGs for any subject. Sponsor's Table 6 and Table 7 summarize heart rate and QTc, respectively, by dose group.

TABLE 6
ANALYSIS OF HEART RATES

PARAMETER DOSE	TIME	SUMMARY VALUES				CHANGE FROM BASELINE					WILCOXON	
		MEAN	S.D.	N	MEDIAN	MEAN	S.D.	N	T-TEST	MEDIAN		
ATRIAL RATE PLACEBO	0	62	8	10	62							
	2	58	8	10	58	-4	6	10	*	-4		
	4	56	8	10	59	-4	8	10		-3		
	8	61	10	10	63	-1	11	10		-1		
	24 POST	59 66	12 8	10 10	58 66	-3 4	7 5	10 10	*	-4 5		
100 MG	0	58	9	6	60							
	2	62	9	6	62	3	6	6		2		
	4	62	4	6	61	4	7	6		3		
	8	64	11	6	65	6	4	6	**	7	*	
	24 POST	62 68	9 6	6 6	62 66	4 10	5 8	6 6	*	3 11		
200 MG	0	53	7	6	53							
	2	55	8	6	55	2	10	6		0		
	4	54	6	6	56	1	11	6		0		
	8	69	19	6	63	16	18	6		9		
	24 POST	55 60	6 6	6 6	53 60	2 7	7 6	6 6	*	4 8		
250 MG	0	48	10	6	44							
	2	55	12	6	54	7	5	6	*	6	*	
	4	54	8	6	54	6	7	6		6	*	
	8	58	9	6	56	10	2	6	**	10	*	
	24 POST	51 60	9 14	6 6	47 55	3 12	3 4	6 6	**	5 11	*	
300 MG	0	54	5	12	54							
	2	54	6	12	53	0	5	12		-1		
	4	55	6	12	55	1	6	12		0		
	8	64	8	12	62	10	10	12	**	8	**	
	24 POST	60 57	9 8	12 12	61 57	7 4	8 7	12 12	*	6 2	*	

* : STATISTICALLY SIGNIFICANT AT P <= 0.05.
** : STATISTICALLY SIGNIFICANT AT P <= 0.01.

TABLE 6
ANALYSIS OF HEART RATES

PARAMETER DOSE	TIME	SUMMARY VALUES				CHANGE FROM BASELINE					WILCOXON	
		MEAN	S.D.	N	MEDIAN	MEAN	S.D.	N	T-TEST	MEDIAN		
VENTRICULAR RATE PLACEBO	0	62	8	10	62							
	2	58	8	10	58	-4	6	10	*	-4		
	4	56	8	10	59	-4	8	10		-3		
	8	61	10	10	63	-1	11	10		-1		
	24 POST	59 66	12 8	10 10	58 66	-3 4	7 5	10 10	*	-4 5		
100 MG	0	58	9	6	60							
	2	62	9	6	62	3	6	6		2		
	4	62	4	6	61	4	7	6		3	*	
	8	64	11	6	65	6	4	6	**	7	*	
	24 POST	62 68	9 6	6 6	62 66	4 10	5 8	6 6	*	3 11		
200 MG	0	53	7	6	53							
	2	55	8	6	55	2	10	6		0		
	4	54	6	6	56	1	11	6		0		
	8	69	19	6	63	16	18	6		9		
	24 POST	55 60	6 6	6 6	53 60	2 7	7 6	6 6	*	4 8		
250 MG	0	48	10	6	44							
	2	55	12	6	54	7	5	6	*	6	*	
	4	54	8	6	54	6	7	6		6	*	
	8	58	9	6	56	10	2	6	**	10	*	
	24 POST	51 60	9 14	6 6	47 55	3 12	3 4	6 6	**	5 11	*	
300 MG	0	54	5	12	54							
	2	54	6	12	53	0	5	12		-1		
	4	55	6	12	55	1	6	12		0		
	8	64	8	12	62	10	10	12	**	8	**	
	24 POST	60 57	9 8	12 12	61 57	7 4	8 7	12 12	*	6 2	*	

* : STATISTICALLY SIGNIFICANT AT P <= 0.05.
** : STATISTICALLY SIGNIFICANT AT P <= 0.01.

TABLE 7
ANALYSIS OF ECG INTERVALS

PARAMETER DOSE	TIME	SUMMARY VALUES				CHANGE FROM BASELINE				WILCOXON
		MEAN	S.D.	N	MEDIAN	MEAN	S.D.	N	T-TEST	
QT CORRECTED PLACEBO	0	0.37	0.02	10	0.37					
	2	0.37	0.02	10	0.38					
	4	0.37	0.02	10	0.37	-0.01	0.02	10		-0.00
	8	0.38	0.03	10	0.37	-0.01	0.03	10		-0.00
	24	0.37	0.03	10	0.37	-0.01	0.02	10		-0.01
	POST	0.38	0.01	10	0.38	0.01	0.02	10	*	0.01
100 MG	0	0.37	0.03	6	0.37					
	2	0.40	0.03	6	0.40	0.02	0.03	6		0.02
	4	0.38	0.02	6	0.38	0.01	0.03	6		0.01
	8	0.39	0.02	6	0.39	0.02	0.03	6		0.02
	24	0.37	0.03	6	0.37	0.00	0.04	6		0.01
	POST	0.40	0.02	6	0.40	0.02	0.04	6		0.03
200 MG	0	0.38	0.02	6	0.38					
	2	0.38	0.03	6	0.38	0.00	0.04	6		-0.00
	4	0.37	0.03	6	0.36	-0.01	0.04	6		-0.01
	8	0.38	0.03	6	0.37	-0.00	0.03	6		-0.00
	24	0.35	0.02	6	0.35	-0.03	0.02	6	**	-0.03
	POST	0.37	0.02	6	0.37	-0.02	0.02	6	**	-0.02
250 MG	0	0.35	0.02	6	0.36					
	2	0.38	0.02	6	0.38	0.02	0.01	6	*	0.02
	4	0.37	0.01	6	0.38	0.02	0.02	6		0.01
	8	0.38	0.02	6	0.38	0.03	0.01	6	**	0.03
	24	0.36	0.03	6	0.37	0.01	0.02	6		0.00
	POST	0.39	0.03	6	0.38	0.03	0.02	6	**	0.03
300 MG	0	0.37	0.02	12	0.38					
	2	0.37	0.02	12	0.37	0.00	0.02	12		0.00
	4	0.38	0.02	12	0.39	0.01	0.02	12		0.01
	8	0.40	0.02	12	0.40	0.02	0.02	12	**	0.03
	24	0.38	0.02	12	0.38	0.00	0.02	12		0.01
	POST	0.38	0.02	12	0.39	0.01	0.02	12		0.01

* : STATISTICALLY SIGNIFICANT AT P <= 0.05.
** : STATISTICALLY SIGNIFICANT AT P <= 0.01.

Reviewer's Comments: ECG tracings from 837-009 (attachment 15, SDN022) and Electrocardiogram report (appendix I in the study report) were reviewed. There were some limitations with interpretation because the ECGs were scanned paper tracings. Based on a random review of a subset of ECGs, they appear adequate for analysis of QT outlier, exclusion of large QT effects, and interpretation of rate and rhythm abnormalities. The only irregular rhythm reported was sinus arrhythmia. No clinically significant ECG changes were reported for any subject.

ECG Analysis by eRT

Originally, all ECGs were recorded with the same model of electrocardiograph, and the QT intervals were measured by hand on the original paper recordings. For the re-analysis, the sponsor reports that QT interval and ventricular heart rate (HR) data for each subject at all time points were hand entered from the original data listings for statistical analysis in SAS. Imiquimod and S26704 serum concentration data for each subject were entered for concentration and response modeling. Using average of pre-study and study day 1 hour 0 as baseline, changes in QTcF interval data were reanalyzed presented in Table 2, Appendix 3 of the Type A Meeting package submitted by Graceway dated November 6, 2009. There was no pattern suggesting a dose-related change. Most changes were less than 30 ms (see below).

Table 2: Summary of Subjects with QTc Value within Pre-Specified Ranges by Visit
(Population: ITT)

Parameter Timepoint Category	100 (N=6)	200 (N=6)	250 (N=6)	300 (N=12)	Placebo (N=10)
QTcF (msec)					
Pre Study					
≤ 450 msec	6 (100.0)	6 (100.0)	6 (100.0)	12 (100.0)	10 (100.0)
> 450 - ≤ 480 msec	0	0	0	0	0
> 480 - ≤ 500 msec	0	0	0	0	0
> 500 msec	0	0	0	0	0
QTcF (msec)					
Day 1 Hour 0					
≤ 450 msec	6 (100.0)	6 (100.0)	6 (100.0)	12 (100.0)	10 (100.0)
> 450 - ≤ 480 msec	0	0	0	0	0
> 480 - ≤ 500 msec	0	0	0	0	0
> 500 msec	0	0	0	0	0
QTcF (msec)					
Day 1 Hour 2					
≤ 450 msec	6 (100.0)	6 (100.0)	6 (100.0)	12 (100.0)	10 (100.0)
> 450 - ≤ 480 msec	0	0	0	0	0
> 480 - ≤ 500 msec	0	0	0	0	0
> 500 msec	0	0	0	0	0
QTcF (msec)					
Day 1 Hour 4					
≤ 450 msec	6 (100.0)	6 (100.0)	6 (100.0)	12 (100.0)	10 (100.0)
> 450 - ≤ 480 msec	0	0	0	0	0
> 480 - ≤ 500 msec	0	0	0	0	0
> 500 msec	0	0	0	0	0
QTcF (msec)					
Day 1 Hour 8					
≤ 450 msec	6 (100.0)	6 (100.0)	6 (100.0)	12 (100.0)	10 (100.0)
> 450 - ≤ 480 msec	0	0	0	0	0
> 480 - ≤ 500 msec	0	0	0	0	0
> 500 msec	0	0	0	0	0
QTcF (msec)					
Day 1 Hour 24					
≤ 450 msec	6 (100.0)	6 (100.0)	6 (100.0)	12 (100.0)	10 (100.0)
> 450 - ≤ 480 msec	0	0	0	0	0
> 480 - ≤ 500 msec	0	0	0	0	0
> 500 msec	0	0	0	0	0
QTcF (msec)					
Post Study					
≤ 450 msec	6 (100.0)	6 (100.0)	6 (100.0)	12 (100.0)	10 (100.0)
> 450 - ≤ 480 msec	0	0	0	0	0
> 480 - ≤ 500 msec	0	0	0	0	0
> 500 msec	0	0	0	0	0

Table 3: Summary of Subjects with Change from Baseline in QTc Value within Pre-Specified Ranges by Visit
(Population: ITT)

Parameter Timepoint Category	100 (N=6)	200 (N=6)	250 (N=6)	300 (N=12)	Placebo (N=10)
Change from Baseline in QTcF (msec)					
Day 1 Hour 2					
≤ 30 msec	4 (66.7)	4 (66.7)	6 (100.0)	12 (100.0)	9 (90.0)
> 30 - ≤ 60 msec	2 (33.3)	2 (33.3)	0	0	1 (10.0)
> 60 msec	0	0	0	0	0
Change from Baseline in QTcF (msec)					
Day 1 Hour 4					
≤ 30 msec	6 (100.0)	5 (83.3)	6 (100.0)	12 (100.0)	10 (100.0)
> 30 - ≤ 60 msec	0	1 (16.7)	0	0	0
> 60 msec	0	0	0	0	0
Change from Baseline in QTcF (msec)					
Day 1 Hour 8					
≤ 30 msec	5 (83.3)	6 (100.0)	6 (100.0)	10 (83.3)	9 (90.0)
> 30 - ≤ 60 msec	1 (16.7)	0	0	2 (16.7)	1 (10.0)
> 60 msec	0	0	0	0	0
Change from Baseline in QTcF (msec)					
Day 1 Hour 24					
≤ 30 msec	5 (83.3)	6 (100.0)	6 (100.0)	12 (100.0)	10 (100.0)
> 30 - ≤ 60 msec	1 (16.7)	0	0	0	0
> 60 msec	0	0	0	0	0
Change from Baseline in QTcF (msec)					
Post Study					
≤ 30 msec	5 (83.3)	6 (100.0)	5 (83.3)	11 (91.7)	10 (100.0)
> 30 - ≤ 60 msec	1 (16.7)	0	1 (16.7)	1 (8.3)	0
> 60 msec	0	0	0	0	0

Source: Appendix 3, Type A meeting package

Reviewer's Comments: There does not appear to be significant effects of imiquimod on the QT interval. Specifically, no subject had an absolute QTcF over 450 ms post-treatment at exposures over 100-fold compared to the topical preparation.

Assessment of Available Data on Heart Rate

Source: Attachment 17, SDN 022 to NDA 22483 dated January 29, 2010

Graceway identified 2 studies (R-837-009 and R-837-019) which assess various doses of imiquimod along with serial heart rate (ECG) measures and time-matched imiquimod exposure data. Five other studies (4 topical R-837T-003, -004, 005, -008, and one oral dose study R-837-018) include ECG measures that were not time-matched to assessments of imiquimod exposures. The two oral dose studies with time-matched assessments of heart rate are described. Data for each study are presented by dose group over time. Heart rate data are the ventricular rates from each subject at each designated time point. For both studies, the atrial and ventricular rates were identical for each subject at each ECG time point. Outlier analyses are also presented for each study. Bradycardic outliers are subjects who experienced a decrease in heart of <50 beats per minute with a > 25% decrease from baseline, at any time point. Tachycardic outliers are subjects who experienced a heart rate >100 beats per minute with a > 25% increase above baseline at any time point.

The design for Study 837-009 has already been discussed. Study R-837-019 was a Phase 1, single-blind, placebo-controlled, single oral dose study conducted in three separate cohorts of eight healthy male adults. The study design is similar to that of the Study R-837-009 and its objective was to examine the time course of a potential antiviral effect induced after

administration of a single oral dose of imiquimod at three dose levels (100, 200, or 300 mg). Within each cohort, 6 subjects received oral imiquimod and 2 subjects received placebo on a randomized basis.

The sponsor reported that inspection of the results from Study R-837-009 suggested a slight increase in heart rate from baseline levels in all imiquimod dose groups, most notably at hours 4 and 8. There was no clear dose effect. The placebo groups evidenced slight decreases in heart rate from baseline.

Reviewer's Comments: The results (Table 1.2 in attachment 17) were reviewed. The Sponsor's interpretation of Table 6 in the original study report is reasonable.

The sponsor reported that results from Study R-837-019 suggested a slight increase in heart rate from baseline level in the 200 and 300 mg dose groups at the eight hour time point after dosing (see Table 1 from attachment 17 below); this slight increase was seen also in the 300 mg dose group at hour 24 after oral dosing. There were no demonstrable increases in heart rate in either the 100-mg or placebo dose groups.

Imiquimod R-837-019

Table 1: Summary of Heart Rate (bpm) by Visit

Ventricular Rate (bpm)	Value	Dose Group			
		100 mg (N=6)	200 mg (N=6)	300 mg (N=6)	Placebo (N=6)
Baseline*	N	6	6	6	6
	Mean	55.9	61.0	58.9	53.6
	SD	8.8	8.2	8.7	6.6
	Median	55.3	58.8	58.5	54.0
	Min	44.0	50.5	48.5	45.5
	Max	69.0	72.5	71.5	63.0
Time-Point: Hour 2	N	6	6	6	6
	Mean	52.0	57.2	53.8	49.2
	SD	8.2	7.2	7.5	3.8
	Median	49.0	56.5	55.0	48.5
	Min	43.0	48.0	45.0	44.0
	Max	66.0	66.0	65.0	54.0
Chg from Baseline to Hour 2	N	6	6	6	6
	Mean	-3.9	-3.8	-5.1	-4.4
	SD	2.5	4.4	3.7	5.8
	Median	-3.5	-3.8	-4.3	-3.0
	Min	-8.5	-8.5	-11.5	-15.0
	Max	-1.0	3.5	-1.0	2.0
Time-Point: Hour 4	N	6	6	6	6
	Mean	51.8	58.5	57.2	52.0
	SD	8.0	8.1	8.1	8.2
	Median	50.0	59.0	61.0	50.5
	Min	43.0	45.0	46.0	44.0
	Max	65.0	68.0	65.0	64.0
Chg from Baseline to Hour 4	N	6	6	6	6
	Mean	-4.1	-2.5	-1.8	-1.6
	SD	5.4	2.7	4.7	4.5
	Median	-4.0	-3.3	-2.8	-1.8
	Min	-11.5	-5.5	-6.5	-7.0
	Max	4.0	1.5	5.0	6.0

Time-Point: Hour 8	N	6	6	6	6
	Mean	54.0	67.2	68.3	52.7
	SD	7.1	9.7	8.2	8.0
	Median	51.5	62.5	67.5	52.0
	Min	46.0	60.0	58.0	43.0
	Max	65.0	83.0	79.0	62.0
Chg from Baseline to Hour 8	N	6	6	6	6
	Mean	-1.9	6.2	9.4	-0.9
	SD	2.6	10.0	8.2	6.1
	Median	-1.5	4.8	10.3	0.8
	Min	-5.5	-7.5	-1.5	-10.0
	Max	2.0	23.0	19.0	7.0
Time-Point: Post Study (Hour 24)	N	6	6	6	6
	Mean	54.0	63.8	66.8	54.5
	SD	9.7	8.5	13.5	8.3
	Median	50.0	62.0	65.5	50.5
	Min	46.0	53.0	53.0	46.0
	Max	73.0	77.0	89.0	66.0
Chg from Baseline to Post Study (Hour 24)	N	6	6	6	6
	Mean	-1.9	2.8	7.9	0.9
	SD	4.7	3.5	10.8	7.9
	Median	-1.5	2.8	5.3	1.8
	Min	-8.5	-2.5	-1.5	-12.0
	Max	4.0	8.0	29.0	9.0

* Baseline values are the mean of the Pre-Study and Pre-Dose ECGs.

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The outlier analyses (as shown in table 2.2 from attachment 17 below) for both studies did not identify any bradycardic or tachycardic outliers for any dose groups at any time points.

Imiquimod R-837-009

Table 2.2: Summary of Subjects with Bradycardic Events* by Visit

Timepoint	100 mg (N=6)	200 mg (N=6)	250 mg (N=6)	300 mg (N=12)	Placebo (N=10)
Hour 2					
No	6 (100.0)	6 (100.0)	6 (100.0)	12 (100.0)	10 (100.0)
Yes	0	0	0	0	0
Hour 4					
No	6 (100.0)	6 (100.0)	6 (100.0)	12 (100.0)	10 (100.0)
Yes	0	0	0	0	0
Hour 8					
No	6 (100.0)	6 (100.0)	6 (100.0)	12 (100.0)	9 (90.0)
Yes	0	0	0	0	1 (10.0)
Hour 24					
No	6 (100.0)	6 (100.0)	6 (100.0)	12 (100.0)	9 (90.0)
Yes	0	0	0	0	1 (10.0)
Post Study (Hour 48)					
No	6 (100.0)	6 (100.0)	6 (100.0)	12 (100.0)	10 (100.0)
Yes	0	0	0	0	0

* A subject had a bradycardic event if any ventricular heart rate value for that time point is < 50 bpm and represents a > 25% decrease from baseline. Baseline values are the mean of the Pre-Study and Pre-Dose ECGs.

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Imiquimod R-837-019

Table 2: Summary of Subjects with Bradycardic Events* by Visit

Timepoint Bradycardic Category	100 mg (N=6)	200 mg (N=6)	300 mg (N=6)	Placebo (N=6)
Hour 2				
No	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)
Yes	0	0	0	0
Hour 4				
No	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)
Yes	0	0	0	0
Hour 8				
No	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)
Yes	0	0	0	0
Post Study (Hour 24)				
No	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)
Yes	0	0	0	0

* A subject had a bradycardic event if any heart rate value for that time point is < 50 bpm and represents a > 25% decrease from baseline. Baseline values are the mean of the Pre-Study and Pre-Dose ECGs.

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Imiquimod R-837-009

Table 3.2: Summary of Subjects with Tachycardic Events* by Visit

Timepoint Tachycardic Category	100 mg (N=6)	200 mg (N=6)	250 mg (N=6)	300 mg (N=12)	Placebo (N=10)
Hour 2					
No	6 (100.0)	6 (100.0)	6 (100.0)	12 (100.0)	10 (100.0)
Yes	0	0	0	0	0
Hour 4					
No	6 (100.0)	6 (100.0)	6 (100.0)	12 (100.0)	10 (100.0)
Yes	0	0	0	0	0
Hour 8					
No	6 (100.0)	6 (100.0)	6 (100.0)	12 (100.0)	10 (100.0)
Yes	0	0	0	0	0
Hour 24					
No	6 (100.0)	6 (100.0)	6 (100.0)	12 (100.0)	10 (100.0)
Yes	0	0	0	0	0
Post Study (Hour 48)					
No	6 (100.0)	6 (100.0)	6 (100.0)	12 (100.0)	10 (100.0)
Yes	0	0	0	0	0

* A subject had a tachycardic event if any ventricular heart rate value for that time point is > 100 bpm and represents a > 25% increase from baseline. Baseline values are the mean of the Pre-Study and Pre-Dose ECGs.

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Imiquimod R-837-019

Table 3: Summary of Subjects with Tachycardic Events* by Visit

Timepoint Tachycardic Category	100 mg (N=6)	200 mg (N=6)	300 mg (N=6)	Placebo (N=6)
Hour 2				
No	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)
Yes	0	0	0	0
Hour 4				
No	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)
Yes	0	0	0	0
Hour 8				
No	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)
Yes	0	0	0	0
Post Study (Hour 24)				
No	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)
Yes	0	0	0	0

* A subject had a tachycardic event if any heart rate value for that time point is > 100 bpm and represents a > 25% increase from baseline. Baseline values are the mean of the Pre-Study and Pre-Dose ECGs.

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Reviewer's Comments: Increases in HR were noted in both studies following single oral doses of imiquimod, which give >100-fold greater imiquimod exposures than imiquimod cream 3.75%. This does not seem to be clinically significant most HR values are around 70 bpm or less which

is reassuring. The changes in HR do not appear to be dose-related. There were no tachycardic or bradycardic outliers.

Assessment of Potential Symptomatic Tachyarrhythmia

Source: Attachment 17, SDN 022 to NDA 22483 dated January 29, 2010

A review of the clinical trial safety database, “Analysis of Adverse Events from 3M Sponsored Clinical Studies of Topical Imiquimod,” was previously submitted to NDA 20-723 (18 April 2005 Amendment to Pending Labeling Supplement 018) in response to a request on March 17, 2005. In this review, event information was pooled across all completed Phase II and III clinical studies for which data was available; some Phase I studies were also included. Since this analysis was conducted, additional placebo-controlled sponsored studies of topical imiquimod 5% cream have been conducted. Some of these studies have been included in the updated analyses. The sponsor reports that certain placebo controlled studies were not included in the analyses because they were mechanism of action studies or involved a special population (solid organ transplant). Since databases were not available for all studies, frequencies were derived from adverse event tables from available clinical study reports. In these studies, adverse events also were coded using 3M modified WHOART.

When the incidences were combined, no imbalance was observed in terms that might be indicative of a risk of a tachyarrhythmia in association with imiquimod treatment (see Sponsor’s table-Appendix 6 from attachment 16 to SDN 022).

Appendix 6: Summary of Imiquimod AE Data
Controlled Clinical Trials - Combined

AE Term	Group	Events	Sample	Rate (%)	P-value
ANGINAL PAIN [Angina pectoris, Prinzmetal Angina]	Imiquimod	3	8464	0.035	1.000
	Placebo	1	3129	0.032	
ARRHYTHMIA	Imiquimod	15	8464	0.177	0.632
	Placebo	7	3129	0.224	
ARRHYTHMIA ATRIAL	Imiquimod	0	8464	0.000	1.000
	Placebo	0	3129	0.000	
ARRHYTHMIA VENTRICULAR	Imiquimod	2	8464	0.024	1.000
	Placebo	0	3129	0.000	
CARDIAC ARREST	Imiquimod	1	8464	0.012	1.000
	Placebo	0	3129	0.000	
CARDIAC FAILURE [Cardiac failure congestive]	Imiquimod	7	8464	0.083	1.000
	Placebo	2	3129	0.064	
CHEST PAIN	Imiquimod	12	8464	0.142	0.136
	Placebo	9	3129	0.288	
DEZZINESS	Imiquimod	66	8464	0.780	0.102
	Placebo	15	3129	0.479	
DYSPNEA	Imiquimod	2	8464	0.024	1.000
	Placebo	1	3129	0.032	
FIBRILLATION ATRIAL	Imiquimod	12	8464	0.142	0.313
	Placebo	7	3129	0.224	
HYPOTENSION	Imiquimod	2	8464	0.024	0.296

Terms listed in all capitals are 3M modified WHOART considered to be relevant to the inquiry by Graceway. Terms listed in lower case and in brackets are MedDRA terms, alone or grouped with a 3M WHOART term.

In original 2005 review, syncope and tachycardia supraventricular appeared twice, tabulated under two different body systems. In this table, the number of subjects listed under each body system were combined to determine an overall frequency.

Pain includes only events mapped to Cardiovascular body system. P value calculated using Fisher’s exact test.

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Appendix 6: Summary of Imiquimod AE Data
Controlled Clinical Trials - Combined

AE Term	Group	Events	Sample	Rate (%)	P-value
	Placebo	2	3129	0.064	
MYOCARDIAL INFARCTION [Acute myocardial infarction]	Imiquimod	3	8464	0.035	1.000
	Placebo	1	3129	0.032	
MYOCARDIAL ISCHAEMIA	Imiquimod	0	8464	0.000	0.270
	Placebo	1	3129	0.032	
PAIN	Imiquimod	0	8464	0.000	0.270
	Placebo	1	3129	0.032	
PALPITATION	Imiquimod	9	8464	0.106	1.000
	Placebo	3	3129	0.096	
PULMONARY OEDEMA	Imiquimod	1	8464	0.012	1.000
	Placebo	0	3129	0.000	
SYNCOPE	Imiquimod	7	8464	0.083	1.000
	Placebo	2	3129	0.064	
TACHYCARDIA	Imiquimod	8	8464	0.095	1.000
	Placebo	2	3129	0.064	
TACHYCARDIA SUPRAVENTRICULAR	Imiquimod	0	8464	0.000	0.020
	Placebo	3	3129	0.096	
[Presyncope]	Imiquimod	1	8464	0.012	1.000
	Placebo	0	3129	0.000	
TACHYCARDIA VENTRICULAR [Ventricular tachycardia]	Imiquimod	2	8464	0.024	1.000
	Placebo	0	3129	0.000	

Terms listed in all capitals are 3M modified WHOART considered to be relevant to the inquiry by Graceway. Terms listed in lower case and in brackets are MedDRA terms, alone or grouped with a 3M WHOART term.

In original 2005 review, syncope and tachycardia supraventricular appeared twice, tabulated under two different body systems. In this table, the number of subjects listed under each body system were combined to determine an overall frequency.

Pain includes only events mapped to Cardiovascular body system. P value calculated using Fisher's exact test.

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Reviewer's Comments: The incidence of cardiac AEs related to rate and rhythm disturbances was similar to placebo and possibly represents the background rate of these events. Rare drug related AEs are most likely to be noted in post-marketing surveillance. As already noted in our previous review dated January 7, 2010, an MGPS data mining analyses of AERS for AEs of concern indicated incidence similar to background rate and OSE also raised no issues of concern in their review.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/

CHRISTINE E GARNETT
03/01/2010

SUCHITRA M BALAKRISHNAN
03/01/2010

NORMAN L STOCKBRIDGE
03/01/2010

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

******Pre-decisional Agency Information******

Memorandum

Date: February 26, 2010

To: Kelisha Turner, Regulatory Project Manager
Milena Lolic, MD, Clinical Reviewer
Jill Lindstrom, MD, Clinical Team Leader
Division of Dermatologic and Dental Products (DDDP)

From: Andrew Haffer, PharmD, Regulatory Review Officer
Shefali Doshi, MD, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: NDA 22-483

DDMAC labeling comments for Zyclara (imiquimod) Cream, 3.75%

In response to DDDP's February 25, 2010 consult request, DDMAC has reviewed the draft labeling (PI and PPI) for Zylcara (imiquimod) Cream, 3.75% (NDA 22-483). DDMAC's comments on the PI and PPI are based on the proposed draft marked-up labeling titled "draft-labeling-text 1-29-2010.doc" that was sent by Kelisha Turner via email on 2/25/10.

DDMAC's comments are provided directly in the document attached (see below). Please note that many of DDMAC's comments on the PI and PPI are similar to comments previously provided on September 9, 2009.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions regarding the PI, please contact Andrew Haffer at 301.796.2268 or Andrew.Haffer@fda.hhs.gov. If you have any questions regarding the PPI, please contact Shefali Doshi at 301.796.1780 or Shefali.Doshi@fda.hhs.gov.

13 pages 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

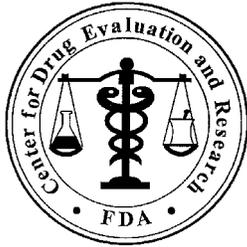
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHEFALI S DOSHI

02/26/2010

We hid the formatting changes so our comments are easier to read.



**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: November 4, 2009

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

Thru: Kellie Taylor, PharmD, Team Leader
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Division of Medication Error Prevention and Analysis

From: Cathy A. Miller, MPH, RN, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Zyclara (Imiquimod) Cream
3.75%

Application Type/Number: NDA 22-483

Applicant/Applicant: Graceway Pharmaceuticals, LLC

OSE RCM #: 2009-172

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1 INTRODUCTION

This review is written in response to a July 28, 2009 request from the Division of Dermatological and Dental Products for an evaluation of the container labels, carton and package insert labeling for Zyclara (Imiquimod) Cream, 3.75%, new drug application (NDA 22-483) to identify areas that could lead to medication errors. This request follows the Applicant's submission of a chemistry supplement dated July 17, 2009 for the pending application.

1.1 PRODUCT INFORMATION

The Applicant currently markets Imiquimod 5% cream under the proprietary name, Aldara, which was approved February 27, 1997. Aldara is indicated for the treatment of actinic keratoses, superficial basal cell carcinoma and external genital warts. Aldara 5% cream has three varying administration regimens (twice weekly, three times weekly and five times weekly) depending on the indication of use.

Zyclara (Imiquimod) 3.75 % Cream, is indicated for the topical treatment of clinically typical visible or palpable actinic keratoses of the face or balding scalp in immunocompetent adults. Zyclara is applied once daily to the skin of the affected area (either the face or balding scalp) at bedtime for two 2-week treatment cycles separated by a 2-week no-treatment period. It is recommended that the treatment area be washed with mild soap and water eight hours following application. Zyclara is supplied in single-use packets, each containing 250 mg of cream, equivalent to 9.4 mg of Imiquimod. Up to two packets may be applied topically to the treatment area.

2 METHODS AND MATERIALS

Using Failure Mode and Effects Analysis,¹ the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the container label, carton labeling and insert labeling submitted by the Applicant on July 17, 2009 to identify vulnerabilities that could lead to medication errors. The submission included container label packet, carton labeling for folded sachet housing card and carton labeling for cycle pack sleeve (see Appendix A through C) as well as the draft Zyclara package insert labeling.

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) SELECTION OF CASES

Since Imiquimod cream is currently marketed under the trade name 'Aldara' in a 5% strength, a search of the Adverse Event Reporting System (AERS) database was performed to identify medication errors that exist with the Imiquimod product line and could be mitigated by changes in labels and labeling. We performed a search of the AERS database on August 18, 2009 using the active ingredient "Imiquimod", tradename "Aldara" and the verbatim terms "Aldara%" and "Imiquimod%". The MedDRA Higher Level Group Term (HLGT) "Medication Errors" and Preferred Term (PT) "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

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

cases that did describe a medication error were categorized by type of error. Additionally, DMEPA currently has a forthcoming postmarketing review of Aldara 5% Cream in process which will review all Aldara cases more extensively (OSE Review #2008-785).

3 RESULTS

3.1 ADVERSE EVENT REPORTING SYSTEM (AERS) CASES

The AERS search strategy retrieved a total of 29 reports involving Aldara. Of the 29 reports, seven reports were deemed not relevant for the following reasons: potential name confusion between Aldara and Alora (n=2), product complaint lack of effect (n=1) and adverse event reports including accidental exposure to the eye after facial administration (n=2), flu-like symptoms (n=1), and irritation at the application site (n=1).

The remaining 22 cases were deemed relevant to Imiquimod product labeling because they involved medication errors and/or adverse events associated with maladministration of Aldara cream (e.g. wrong frequency, wrong dose and wrong site). In 21 of the 22 cases, adverse events were reported along with maladministration of Aldara including skin site irritation, skin redness and swelling, extreme pain at the application site, skin burning and scabbing, ulceration, erythema, vulvar necrosis, nose bleeds from exposure to the nasal cavity, flu-like symptoms, fever, malaise, headaches, painful urination, nausea, frequent loose stools, bloody stool, stomach pain and swelling, arthralgia, stiff neck, whole body pain, chest pain, severe leg cramps, enlarged lymph nodes, eye irritation and redness, blurred vision, minor lip swelling and dizziness.

3.1.1 Patient Complaint (No Medication Error) (n=1)

In one of the 22 cases, no medication error is cited in the report, however, the reporter states she was prescribed Aldara for the treatment of genital warts but she was never provided instructions on proper dose or administration technique by the prescribing doctor or the dispensing pharmacist. The patient complained of a variety of adverse events following two consecutive days of administration including fever of 102 degrees, stinging at application site, onset of migraine headache and flu-like symptoms. The patient was re-evaluated and discontinued the treatment. No additional information was provided regarding the prescribing physician or dispensing pharmacist for this case.

3.1.2 Wrong Frequency and/or Wrong Dose (n=18)

Eighteen of the 22 cases involved wrong frequency and/or wrong dose medication errors.

One of the 18 cases involved a wrong frequency and wrong dose medication error. The patient had a prescription for Aldara filled at a local pharmacy which included instructions to “apply four times daily for four weeks.” The patient noted the discrepancy on the labeled instructions compared to the products administration instructions and returned to the pharmacy to question the instructions (the patient did not use the product). The pharmacy staff member discovered that the prescription had been written correctly by the ordering physician as “apply four times per week for four weeks”, however, the order was transcribed and labeled incorrectly in the pharmacy. No additional information was provided regarding the order transcription or dispensing pharmacy staff for this case.

In eleven of the 18 cases, wrong frequency medication errors occurred due to the patient’s non-compliance with the prescribed instructions. In one of the eleven cases, the patient’s non-compliance involved underuse of Aldara, applying the crème once per week instead of the prescribed three times per week. No information was provided regarding the patient’s rationale for non-compliance with the use of the product. In the remaining ten cases, the patient applied

Aldara cream more frequently than prescribed for their indication, including one case where the patient reports she misunderstood the instructions to be “three times daily” instead of “three times weekly” and another case where the patient claimed the doctor ordered Aldara to be applied daily however, this claim was not supported by additional information in the report. In all other cases, the reports did not include additional information regarding the root cause of the non-compliance with the prescribed frequency of use.

Six of the 18 cases involved wrong frequency medication errors where the prescribing doctor ordered the frequency incorrectly (e.g. three times daily, wrong days of the week, and prescribing two versus three times per week for labeled indication). In one case, the reporter stated that the prescribing general practitioner may have mixed the three indicated therapies when prescribing, adding more frequent applications, however no additional information was provided in the report regarding the root cause of the error. In another case, the prescribing physician ordered Aldara three times per week to be administered Monday, Tuesday and Wednesday, instead of Monday, Wednesday and Friday, per the insert labeling instructions for genital warts. No adverse events were reported with the maladministration. In the remaining four cases, the physician prescribed Aldara to be administered more frequently than the labeled administration instructions for the indication of use. None of these four cases provided information regarding the root cause of the wrong frequency medication errors that occurred at the prescribing physician level.

3.1.3 Wrong Application Site (n=2)

In two of the 22 cases, wrong application site (maladministration) medication errors occurred due to inadvertent exposure to the wrong site (nasal passage) and administration to adjacent areas of the genitals. In the first case, a patient being treated for actinic keratoses of top of the forehead and was prescribed Aldara five times per week (although the patient admits he occasionally skipped doses). A few weeks after initiating Aldara therapy the patient developed ‘very serious’ nose bleeds that were difficult to stop. After evaluation in the emergency room, the patient stated he had been administering Aldara as directed to his forehead with his finger but was not thorough washing his hands before also administering nasal moisturizer into the nostrils to treat chronic dry sinuses. The treating physician theorized that the patient had inadvertently applied Aldara inside his nose causing irritation and subsequent nose bleeds. The patient was instructed on thoroughly washing his hands with soap and water after each Aldara application. In the second case, a patient that was prescribed Aldara for external genital warts (condyloma) was instructed to apply the cream to one isolated external condyloma located at posterior of the vulva three times weekly. During the second Aldara administration, the patient misused the product, applying the cream to the perineum and anus, in addition to the prescribed site. The patient developed fever, chills, asthenia and nausea, and also experienced edema of the vulva, anal mucosa and ulcerations of the anus. Aldara treatment was discontinued and the patient’s symptoms were treated.

3.1.4 Non-Compliance (n=1)

One of the 22 cases involved a patient’s non-compliance with the prescribed Aldara dose (amount) and administration site. The patient was prescribed Aldara cream for vulvar warts and was instructed to apply a thin layer of cream to the external warts with one packet. The patient reports she applied an additional second packet of cream to the internal part of the labia minora. The patient experienced labial swelling, irritation, and second degree burns. She was treated in the hospital and after examination, was also diagnosed with genital herpes, for which she was treated in addition to discontinuing the Aldara treatment. No additional information was provided regarding the rationale for the patient’s non-compliance with the Aldara administration instructions.

3.2 LABELS AND LABELING

3.2.1 *Zyclara Package Insert Labeling*

- A. Currently, labeling does not include a warning or alert about the use of more than one Imiquimod product.

3.2.2 *Zyclara Single Application Packets Container Label*

- A. The current presentation of the volume (0.25 g) is presented in a bolded, larger font than the product strength (3.75%).

3.2.3 *Zyclara Fold-Out and Cycle Pack Sleeve Carton Labeling*

- A. The frequency of administration is not displayed on the carton labeling. Since Imiquimod is currently marketed in a 5% strength for three indications under the trade name ‘Aldara’ with varying administration instructions, consider adding dosing statement to the principal display panel of the carton labeling providing specific advice as to how frequently Zyclara is administered.
- B. The route of administration statement (b) (4) is incomplete compared to insert labeling instructions that warn against “oral, ophthalmic, or intravaginal use.”
- C. The current presentation of the dosage form (Cream) and the strength (3.75%) appear sequentially out of place. They are currently presented above (before) the proprietary and established name.

4 DISCUSSION

Our evaluation of the postmarketing cases of wrong dose, wrong frequency, and wrong administration site medication errors with the existing Imiquimod 5% (Aldara) product identified patient and prescriber-related sources of error. In some cases, the patient was non-compliant with the prescribed dosing regimen. In other cases, dosing and administration confusion occurred at the physician and pharmacy level that included wrong frequency and/or administration instructions prescribed by the physician and wrong frequency transcribed and labeled by the pharmacy staff. DMEPA acknowledges that the dosing regimens for the various Aldara indications of use are inherently complex, however, we defer final conclusions regarding possible improvements to the Aldara labels and labeling to the assessment presented in the forthcoming Aldara postmarketing review (OSE #2008-785).

Since Zyclara will have similar product characteristics as Aldara, DMEPA surmises that with the introduction of the new product, wrong frequency and concomitant use medication errors may occur and we believe additional measures in the insert labeling, container labels and carton labeling may help to reduce the risk of medication errors. Our concerns and proposed measures are described in detail below.

4.1 ZYCLARA PACKAGE INSERT LABELING

The Aldara maladministration medication errors provide emphasis on the importance adequate product labeling to maximize correct dosing and administration of Imiquimod. Our review of the draft Zyclara package insert labeling found that the indication of use (topical treatment of clinically typical visible or palpable actinic keratoses of the face or balding scalp in immunocompetent adults), along with the dosing and administration instructions (once daily

before bedtime to face or balding scalp) are clearly delineated. However, given the current availability of Imiquimod in a 5% strength and the associated maladministration errors we identified in our AERS search, we feel that added language to labels and labeling may be suitable to advise about the use of multiple Imiquimod-containing products. This added information may provide additional safeguards against potential inadvertent misuse or concomitant use of the Imiquimod-containing products in such a manner that the patient is overexposed to the drug.

4.2 ZYCLARA CONTAINER LABELS AND CARTON LABELING

DMEPA's evaluation of Zyclara carton labeling and container labels found that it may be prudent to provide additional distinction regarding frequency of use and duration of use for Zyclara 3.75% compared to Aldara 5%, by adding language to the principal display panel of the container label and carton labeling that emphasizes "once daily" use. Although the new Imiquimod 3.75% cream will have a different trade name 'Zyclara', both products share the same active ingredient and one overlapping indication of use. This language may serve as an added feature about the product's frequency of use to providers, pharmacy staff and patients who are already familiar with Aldara, and help avert wrong frequency medication errors.

Additionally, presentation of the product volume (0.25 g) on the Zyclara packet container label appears larger and bolder than the product strength (3.75%). The product volume should not be presented more prominently than the product strength. Since the introduction of Zyclara 3.75% will add a second strength to the Imiquimod cream product line, it is important to provide adequate prominence to the strength on labels and labeling without distracting from the readability of this information.

The Applicant's presentation of dosage form and product strength on Zyclara carton labeling is presented sequentially out of order, appearing before (above) the proprietary and established name. This presentation minimizes the visibility of the product strength. Drug products are typically presented on labels and labeling with the order of the proprietary name, established name, dosage form and strength in labeling (e.g. Zyclara Imiquimod Cream, 3.75%). However, the Applicant's current presentation places the dosage form and strength before (above) the proprietary and established name (Cream, 3.75% Zyclara Imiquimod). This information is typically presented adjacent to or below the proprietary and established name to provide maximum readability of this important product information.

Lastly, our review of container labels and carton labeling also revealed that there is discordance between the route of administration information contained in Zyclara insert labeling, which reads "not for oral, ophthalmic or intravaginal use" and the statement that appears on the Zyclara container label and carton labeling which reads [REDACTED] (b) (4) [REDACTED]". Our AERS search of Aldara 5% cream revealed two cases where the patient non-compliantly applied the cream to areas other than the prescribed site (perineum, anus and vulva) as well as accidental exposure to the eye. These cases emphasize the importance of providing adequate information in labels and labeling to maximize the appropriate application of Zyclara while warning against the use in contraindicated areas. Given the medication errors that have already occurred and the discordance between insert labeling language and container labels/carton labeling, this warning information should align to comprehensive instruct on the products' proper use and warn against the product's use in all of these prohibited areas (e.g. Do Not Use...).

5 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation noted an area where information in the container label can be improved to minimize the potential for medication errors. We provide our recommendations for the Division

to consider in section 5.2 Comments to the Applicant. We request the recommendation in Section 5.2 be communicated to the Applicant.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Janet Anderson, OSE Project Manager, at 301-796-0675.

5.1 COMMENTS TO THE DIVISION

The following comments address pending decisions in process between DMEPA and the Division of Dermatology and Dental Products (DDDP) regarding the need for added language to the Zyclara package insert labeling warning about the use of multiple Imiquimod-containing products.

As discussed with DDDP in conjunction with the Applicant's Formal Dispute Resolute Appeal, DMEPA recommends that language be added to both the Aldara and Zyclara (Imiquimod-containing products) insert labeling warning about the use of multiple Imiquimod products, due the risk of overexposure and the associated adverse events.

5.2 COMMENTS TO THE APPLICANT

5.2.1 Zyclara Single Application Packets Container Label

- 1) Decrease the size and prominence of the volume (0.25 g) on the container label packet. The current presentation of the volume (0.25 g) appears larger than the strength (3.75%)
- 2) Revise the route of administration statement that appears on the back of the Zyclara packet container labeling that currently instructs first, on the appropriate application of Zyclara (b) (4). This statement is incomplete in that it does not correlate with the route of administration statement that appears in the Zyclara insert labeling that reads "Zyclara Cream is not for oral, ophthalmic or intravaginal use." Postmarketing medication errors for the currently marketed Imiquimod product, Aldara 5% identified cases involving inadvertent exposure and intentional patient misuse of the product which involve applying the product to areas other than those prescribed areas. This misuse resulted in adverse events including skin irritation, swelling, vulvar swelling, painful urination, ulceration and pain. Revise the statement to align with the statement as presented in the Zyclara package insert labeling that strongly emphasizes the appropriate route of administration application of Zyclara "For Dermatological Use Only" followed by warning information about contraindication use "Do Not Use on Other Areas Of the Body or Ingest". For example:

For Skin Use Only

Avoid contact with eyes, mouth and other areas of the body

5.2.2 *Zyclara Fold-Out and Cycle Pack Sleeve Carton Labeling*

- 1) To provide added differentiation with the dosing regimen of Zyclara compared to the multiple dosing regimens currently available with the approved Aldara product, consider adding a frequency statement to the principal display panel of the fold-out and pack sleeve carton labeling. For example: For Once Daily Use For Two-Week Treatment Cycles separated by a Two-Week No-Treatment period.
- 2) Revise the route of administration statement that appears on the back of the Zyclara packet container labeling that currently instructs first, on the appropriate application of Zyclara “For Dermatological Use Only – Not for Ophthalmic Use”. This statement is incomplete in that it does not correlate with the route of administration statement that appears in the Zyclara insert labeling that reads “Zyclara Cream is not for oral, ophthalmic or intravaginal use.” Our search of medication errors retrieved from the Adverse Events Reporting System (AERS) database for the currently marketed Imiquimod product, Aldara 5% identified errors involving inadvertent exposure and intentional patient misuse of the product which involve applying the product to areas other than those prescribed areas. This misuse resulted in adverse events including skin irritation, swelling, vulvar swelling, painful urination, ulceration and pain. Revise the statement to align with the statement as presented in the Zyclara package insert labeling that strongly emphasizes the appropriate route of administration application of Zyclara “For Dermatological Use Only” followed by warning information about contraindication use “Do Not Use on Other Areas Of the Body or Ingest”. For example:

For Skin Use Only

Avoid contact with eyes, mouth and other areas of the body

- 3) Relocate the dosage form and strength presentation on the principal display panel of the fold-out and cycle packet carton labeling. The current presentation appears sequentially out of place as it is presented above (before) the proprietary and established name. Drug products are typically presented by proprietary name, established name, dosage form and strength in labeling (e.g. Zyclara Imiquimod Cream, 3.75%). However, the Applicant’s current presentation places the dosage form and strength before (above) the proprietary and established name (Cream, 3.75% Zyclara Imiquimod) . Revise the presentation so that the dosage form (Cream) and the strength (3.75%) appear directly below established name. For example:

Zyclara
(Imiquimod) 3.75% Cream

6 REFERENCES

1. *Adverse Events Reporting System (AERS)*

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufacturers that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported

adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

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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/

CATHY A MILLER
11/04/2009

KELLIE A TAYLOR
11/04/2009

DENISE P TOYER
11/04/2009

CAROL A HOLQUIST
11/04/2009



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 13, 2009

To: Susan J. Walker, MD, Division Director
Division of Dermatological and Dental Products

Through: Claudia Karwoski, PharmD, Division Director
Division of Risk Management (DRISK)
LaShawn Griffiths, RN, MSHS-PH, BSN, Acting Team
Leader Patient Labeling Reviewer
Division of Risk Management

From: Jessica M. Diaz, RN, BSN
Patient Product Information 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 22-483

Applicant/sponsor: Graceway Pharmaceuticals, LLC

OSE RCM #: 2009-174

1 INTRODUCTION

This review is written in response to a request by the Division of Dermatological 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. Please 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 Prescribing Information (PI) submitted April 14, 2009 and revised by the Review Division throughout the current review cycle.
- Draft ZYCLARA (imiquimod) cream Patient Package Insert (PPI) submitted on April 14, 2009.

3 RESULTS OF REVIEW

In our review of the PPI, we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information

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.

|

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/s/

JESSICA M DIAZ
10/13/2009

CLAUDIA B KARWOSKI
10/13/2009
concur

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: September 3, 2009

To: Kelisha Turner, DDDP
Brenda Carr, MD, DDDP
Jill Lindstrom, MD, DDDP

From: Andrew Haffer, PharmD, DDMAC Professional Reviewer
Shefali Doshi, MD, DDMAC DTC Reviewer

Re: NDA# 22-483
Zyclara (imiquimod), Cream, 3.75%

DDMAC has reviewed the draft PI for Zyclara (imiquimod), Cream, 3.75%. DDMAC's comments on the PI are based on the proposed draft labeling titled "NDA 22-483 draft-labeling-text 4-14-09 TEAM MEETING 1 8-10-09.doc" distributed by Kelisha Turner via email on 8/26/09 at 11:06 AM.

DDMAC's comments are provided directly in the attached document (see below).

If you have any questions about DDMAC's comments on the PI please call Andy Haffer. For questions regarding comments on the PPI please call Shefali Doshi.

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/s/

ANDREW S HAFFER
09/09/2009

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 18, 2009

TO: Susan Walker, M.D.
Director
Division of Dermatology and Dental Products (DDDP)
Office of Drug Evaluation III

Dennis Bashaw, Pharm. D.
Director
Division of Clinical Pharmacology III (DCPIII)
Office of Drug Evaluation III

FROM: Arindam Dasgupta, Ph.D.
Division of Scientific Investigations (DSI)

THROUGH: C.T. Viswanathan, Ph.D. *Mart: K. Jan 8/18/2009*
Associate Director (Bioequivalence)
Division of Scientific Investigations (DSI)

SUBJECT: Review of EIR Covering NDA 22-483 Imiquimod 3.75%
Cream from Graceway Pharmaceuticals LLC.

At the request of DCP III, the Division of Scientific Investigations (DSI) audited the clinical and analytical portions of the following bioequivalence study:

Study Number: GW01-0706 [REDACTED] (b) (4)

Study Title: An Open Label, Single Center, Non-Randomized Pharmacokinetic Study to Evaluate Safety of and Systemic Exposure to Multiple Applications of Imiquimod Cream in Subjects with Actinic Keratoses of the Face and/or Balding Scalp.

The audit of the clinical and analytical portions of this study were conducted at Comprehensive Phase I, Fort Myers, Florida and Taylor Technology Inc, Princeton, NJ respectively. **Please note that the analytical portion of the study was conducted at [REDACTED] (b) (4), and all the study related documentation were transferred to [REDACTED] (b) (4) June 2009 after [REDACTED] (b) (4) closed down their operations.**

Following the clinical site inspection at Comprehensive Phase I, (July 13-17, 2009), there was no significant finding and no FDA

Form 483 was issued. Following the analytical inspection at (b) (4) (July 13-17, 2009), Form 483 was issued (attachment 1). Our evaluation of the significant findings are as follows:

Analytical Site: (b) (4)

1. Failure to report all validation experiments containing valid data. For example, a long term stability experiment conducted on August 26, 2008 was not reported.

All completed validation experiments containing valid data should have been reported and discussed. The firm needs to address this concern in their future studies. This finding, however, should not have significant impact on the study outcome as (1) results of August 26, 2008 validation run did not exhibit stability problems and (2) long term stability up to 2 years at -20°C was provided in the 3M Pharmaceutical validation report.

2. Incurred sample reproducibility (ISR) was not conducted for the study.

The reason for not conducting ISR experiment was not documented at the time of the study conduct (August 8-26, 2008). As the firm had an active SOP (effective May 22, 2008) for ISR, ISR assessment should have been conducted to confirm the reproducibility of the pharmacokinetic data generated by the LC/MS/MS method.

3. Stock solutions of R-837 and S-26704 for making calibrators were used after the expiration date based on stability testing.

The firm needs to provide stock solution stability data to cover the duration of sample analysis for R-837 (analyte) and S-26704 (active metabolite).

4. Failure to document and retain records for all aspects of study conduct.

For example, QC samples (low, medium and high) were prepared in bulk, pipetted into 0.800 ml aliquots, frozen and stored at -20 degrees C until use. Although a total of 15 aliquots of QCs were prepared at each level, data audit reveals that a total of 19 aliquots of QC s were used at each level during the course of method validation and subject sample analysis.

The number of QC aliquots said to have been used during the study exceeded the number prepared.

Absence of documentation concerning preparation of all QC samples used during method validation and in analytical runs is of concern and can raise questions on reliability and integrity of the analytical data. The firm needs to provide additional supporting documentation or explanation to account for the discrepancy noted in the above Form 483 observation. The firm should also assure that their current procedures can assure adequate documentation of all study events.

Conclusion:

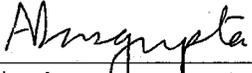
Following the above inspection, the Division of Scientific Investigations recommends the following:

- The firm should conduct an experiment and provide data to confirm incurred samples reproducibility of the LC/MS/MS method used in study GW01-0706 (see Form 483, Item 2).
- The firm needs to provide additional stock solution stability data for R-837 (analyte) and S-26704 (active metabolite) to cover the period of the study (see Form 483, Item 3).
- The firm should provide (1) all documentation or records concerning preparation of QCs used during method validation and in analytical runs and (2) explain why QC aliquots said to have been used during the study exceeded the number prepared (see Form 483, Item 4).

The DCP III reviewer should evaluate the impact of the above recommendations for the study.

At the close of the inspection, the firm indicated that they would provide a written response to all the Form 483 findings. As of the date of this memo, (b)(4) has not submitted a response. Upon receipt of the response, DSI will evaluate and forward a copy of our evaluation to DDDP and DCPIII.

After you have reviewed this transmittal memo, please append it to the original NDA submission.



Arindam Dasgupta, Ph.D.

Final Classifications:

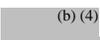
VAI -  (b) (4)

cc: DARRTS
OND/ODE3/DDDP/Walker/Turner
OTS/OCF/DCP3/Bashaw
OC/DSI/Viswanathan/Dasgupta/Yau/Rivera-Lopez

cc: email
CDER DSI PM TRACK

Draft: AD 7/24/09

Edits: MKY 7/30/09

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/s/

ARINDAM DASGUPTA

08/20/2009

Dr. Martin Yau acting for Dr. Viswanathan



**Department of Health and Human Services
Public Health Service
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EXECUTIVE SUMMARY

The Division of Dermatology and Dental Products (DDDP) requested this review after receiving an original NDA submission for imiquimod 3.75% cream (NDA 22-483), a lower concentration than the currently available formulation of imiquimod 5% cream (Aldara Cream, NDA 20-723), for the treatment of actinic keratosis. This review describes post-marketing reports from the Adverse Event Reporting System (AERS) database of lymphoma, pancytopenia, and cardiovascular adverse events of interest (i.e. ischemic heart disease, thromboembolic events, and arrhythmias) with serious outcomes associated with imiquimod 5% cream.

AERS was searched for pancytopenia, lymphoma, and cardiovascular adverse events of interest resulting in serious outcomes associated with imiquimod 5% cream from marketing to June 24, 2009. A data mining analysis of AERS did not identify safety signals related to this review.

We identified only one case in the pancytopenia search, which resulted in hospitalization. However, this case is not suggestive of imiquimod-induced pancytopenia since all three laboratory values relevant to pancytopenia (red blood cells, white blood cells, platelets) occurred over the course of three hospitalizations and were not decreased at the same time during any of the hospitalizations. Additionally, the report stated that the patient underwent multiple venesections and was eventually diagnosed with capillary leak syndrome. We identified eight cases of adverse events related to lymphoma with serious outcomes. One death was reported among this group, which occurred in a patient with a failing renal transplant. Two cases were confounded due to a history of lymphoma (1) and use of imiquimod to treat lymphoma (1).

We identified 15 cases of cardiovascular events of interest (stroke-6, arrhythmia-3, myocardial infarction-2, other-4) with serious outcomes. All six stroke cases reported hospitalization and subsequent discharge; however, in one case, the patient died 26 days later from an unknown cause. All six cases of stroke occurred in elderly patients and were confounded based on medical history and/or concomitant medications. Three cases of arrhythmia were reported; one resulted in death 17 days after imiquimod was discontinued due to an unspecified hepatic disorder and the remaining two reported other serious outcomes; none of these cases reported confounding factors. There were no reports of QT prolongation or Torsades de Pointes; however, one case reported a positive rechallenge resulting in supraventricular tachycardia. Two cases of life-threatening myocardial infarctions were reported in a 59 and 77 year old; however, one case was potentially confounded. Four cases of other cardiovascular events of interest were reported in patients 68 to 80 years of age. Two cases resulted in death following a thromboembolic event; one additional case reported death from an unknown cause. The remaining case reported hospitalization and a positive rechallenge of elevated creatinine phosphokinase.

Based on the case describing a positive rechallenge of a supraventricular tachycardia, it is possible that imiquimod is associated with a risk of arrhythmia; however, arrhythmias are currently listed in the imiquimod label. Analysis of the remaining AERS cases does not suggest any new, compelling post-marketing safety signals for pancytopenia, lymphoma, or cardiovascular events of interest (i.e. ischemic heart disease and thromboembolic events). Since this review did not identify new post-marketing safety signals, DPV has no recommendations for labeling enhancements at this time.

1 BACKGROUND

1.1 INTRODUCTION

The Division of Dermatology and Dental Products (DDDP) requested this review after receiving an original NDA submission for imiquimod 3.75% cream (NDA 22-483), a lower concentration than the currently available formulation of imiquimod 5% cream (Aldara Cream, Graceway Pharmaceuticals LLC). The indication for imiquimod 3.75% cream is actinic keratosis (AK), which is an approved indication for imiquimod 5% cream. Imiquimod 5% cream is also approved for external genital and perianal warts / condyloma acuminata and superficial basal cell carcinoma (sBCC).¹ This review describes post-marketing reports from the AERS database of lymphoma, pancytopenia, and cardiovascular adverse events of interest (i.e. ischemic heart disease, thromboembolic events, and arrhythmias) with serious outcomes associated with imiquimod 5% cream.

A post-marketing safety review completed in 2004 by the Office of Drug Safety (ODS, now the Office of Surveillance and Epidemiology-OSE) described 12 cases of cardiac events and six cases of death in which an association between imiquimod and the events could not be ruled out. However, the cases were not compelling and no labeling recommendations were made.² In 2009, DDDP sent a consult to the Division of Cardiovascular and Renal Products (DCRP) regarding the cardiovascular safety concerns; DCRP agreed with the conclusions in the ODS post-marketing safety review.³ DCRP also conducted a data mining analysis of the Adverse Event Reporting System (AERS) database related to thromboembolism and myocardial ischemia. They concluded that “*the signal scores suggested that the incidence was similar/less than the background rate in the general population;*” however, they recommended that DDDP consult OSE regarding these events.³ (b) (4)



Additionally, at the Mid-Cycle meeting for imiquimod 3.75% cream, DDDP requested that OSE review adverse events related to lymphoma and pancytopenia.

1.2 REGULATORY HISTORY

Imiquimod was FDA approved on February 27, 1997 for the treatment of external genital and perianal warts / condyloma acuminata in adults. Additional relevant label changes include:

- September 3, 2002: Indication expanded to include patients 12 years or older.
- March 2, 2004: Indication expanded to include treatment of clinically typical, nonhyperkeratotic, nonhypertrophic AK on the face or scalp in immunocompetent adults.
- July 14, 2004: Indication expanded to include the treatment of biopsy-confirmed, primary sBCC in immunocompetent adults, with a maximum tumor diameter of 2.0 cm, located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured.
- March 22, 2007: Limitations of Use section stated that studies in children 2-12 years of age with Molluscum Contagiosum failed to demonstrate efficacy.

1.3 PRODUCT LABELING

The approved indications for imiquimod 5% cream, dosing information, and adverse events seen in clinical trials relevant to this review are described in Table 1.

Table 1. Imiquimod indications, dosing information, and relevant adverse events observed in clinical trials.¹

Indication	Relevant Dosing Information	Relevant adverse events observed in clinical trials
AK	Applied 2x/week for 16 weeks to a defined treatment area on the face <u>or</u> scalp (defined as one contiguous area of ~25 cm ²). No more than one packet should be applied to the contiguous treatment area at each application. Left on for ~8 hours.	Atrial fibrillation: imiquimod (3/215, 1%) vs. vehicle (2/221, 1%)
sBCC	Applied 5x/week for 6 weeks to a biopsy-confirmed sBCC. The target tumor should have a maximum diameter of 2 cm. Left on for ~8 hours.	Lymphadenopathy: imiquimod (5/185, 3%) vs. vehicle (1/179, <1%) Chest pain: imiquimod (2/185, 1%) vs. vehicle (0/179, 0%)
External Genital Warts	Applied 3x/week to external genital/perianal warts for a maximum of 16 weeks. The application site should not be occluded. Left on for 6 -10 hours.	---

Additionally, the current imiquimod 5% cream label contains the following information under the Post-marketing Experience section¹:

Cardiovascular: capillary leak syndrome, cardiac failure, cardiomyopathy, pulmonary edema, arrhythmias (tachycardia, atrial fibrillation, palpitations), chest pain, ischemia, myocardial infarction, syncope

Hematological: decreases in red cell, white cell and platelet counts (including idiopathic thrombocytopenic purpura), lymphoma

Although imiquimod is applied topically, systemic absorption has been seen when it was used as indicated. Additionally, systemic reactions have been reported, including flu-like signs and symptoms; these are labeled under the Warning and Precautions section of the label.¹

2 METHODS AND MATERIALS

2.1 AERS SELECTION OF CASES

AERS was searched for pancytopenia, lymphoma, and cardiovascular adverse events of interest (i.e. ischemic heart disease, thromboembolic events, and arrhythmias) resulting in serious outcomes associated with imiquimod. Searches were conducted for adverse event reports from marketing to June 24, 2009 using the drug terms Aldara and imiquimod (including associated trade, generic, and verbatim names). The AERS search retrieved 1630 total adverse event reports associated with imiquimod. Specific adverse event search terms and corresponding results are described below.

2.1.1 PANCYTOPENIA

The AERS search for adverse events related to pancytopenia associated with imiquimod use retrieved one report using the Cytopenia and haematopoietic disorders affecting more than one type of blood cell SMQ (broad search, see Appendix A for a listing of preferred terms).

Case definition for pancytopenia: Cases reporting a decrease in red blood cells, white blood cells, and platelets were included for further analysis.

This case is described in Section 3.1.1 below.

2.1.2 LYMPHOMA

The AERS search for lymphoma associated with imiquimod use retrieved eight reports using the following search terms: Lymphomas Hodgkin's disease (HLGT), Lymphomas NEC (HLGT), Lymphomas non-Hodgkin's B-cell (HLGT), Lymphomas non-Hodgkin's T-cell (HLGT), and Lymphoma's non-Hodgkin's unspecified histology (HLGT).

Case definition for lymphoma: Cases reporting lymphoma were included for further analysis.

These eight cases are described in Section 3.1.2 below.

2.1.3 CARDIOVASCULAR EVENTS

The AERS search for cardiovascular adverse events of interest associated with imiquimod use retrieved 38 reports using the following SMQ (broad searches, see Appendix B for a listing of preferred terms): Ischaemic heart disease, Embolic and thrombotic events, Cardiac arrhythmias, and Torsade de pointes / QT prolongation.

Case definition for cardiovascular events of interest: Cases reporting cardiovascular events related to ischemic heart disease, thromboembolic events, and arrhythmias (with EKG/ Holter monitor findings) were included for further analysis.

Twenty-three cases were not included in the analysis for the following reasons:

- Retrieved in arrhythmia search (e.g. "racing heart"), but without EKG/ Holter monitor findings (9)
- Did not describe cardiovascular events of interest (8)
- Duplicates (4)
- Described under another section in this review: pancytopenia (1), lymphoma (1)

The remaining 15 cases are described in Section 3.1.3 below.

2.2 LITERATURE SEARCH

A PubMed literature search conducted on June 30, 2009 using the search string “imiquimod OR Aldara” and limiting the results to case reports did not identify additional reports of pancytopenia, lymphoma, or cardiovascular adverse events of interest related to imiquimod.

2.3 DATA MINING

A data mining analysis of the AERS database was performed using Empirica Signal[®] software and the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm.^{a,b} MGPS quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting rate of an event for a particular drug relative to all other drugs and events in the database being analyzed. MGPS also calculates lower and upper 90% confidence limits for the EBGM values, denoted EB05 and EB95 respectively.

The data mining analysis was performed using the following criteria:

- Run Name: Generic (S)
- Generic name: imiquimod
- Preferred Terms: all preferred terms
- Date of run: July 1, 2009 (ID number 823; data current as of June 19, 2009)

OSE typically selects an EB05 score of > 2.0 to identify a potential safety concern (i.e. the drug-event combination is reported at least twice the expected rate when considering all other drugs and events in the database). However, for this review, all EB05 scores greater than 0 were included for analysis. Results of the data mining analysis are discussed in Section 3.2.

3 RESULTS

3.1 ADVERSE EVENTS CASES

3.1.1 PANCYTOPENIA

The one case of pancytopenia reported with imiquimod use is summarized below. Of note, this case was also retrieved in the search for cardiovascular events.

ISR 4250028, Foreign (2003): A 56 year old male used imiquimod three times a week overnight to treat AK on his head. Twelve days after starting imiquimod, he was hospitalized due to chest pain, nausea, vomiting, fatigue, and edema of arms and legs. While hospitalized, the following tests were done: coronary angiography (low coronary sclerosis, no coronary heart disease,

^a DuMouchel W, Pregibon D. Empirical bayes screening for multi-item associations. Proceedings of the conference on knowledge discovery and data; 2001 Aug 26-29; San Diego (CA): ACM Press: 67-76.

^b Szarfman A, Machado SG, O’Neill RT. Use of Screening Algorithms and Computer Systems to Efficiently Signal Higher-Than-Expected Combinations of Drugs and Events in the US FDA’s Spontaneous Reports Database. Drug Safety 2002; 25:381-392.

slightly delayed coronary perfusion), arterial digital subtraction angiography (suggested postembolic or postthrombotic syndrome), cardio MRT (no evidence of micro-infarction or coronary cardiac disease), ejection rate was 63%, and iliac crest biopsy (expansion of the erythro- and megakaryopoiesis with empty iron reserves); relevant laboratory values are shown in Table 2. Within four days of admission, he underwent two venesections. He was discharged after a total of nine days on pantoprazole and another unspecified drug for a positive helicobacter fast reaction test. Imiquimod therapy was temporarily interrupted on an unspecified date while he was hospitalized, but subsequently restarted. Fifty-six days after discharge, he was hospitalized again due to **anemia**; additional details regarding this hospitalization were not provided. Fifteen days after the second hospitalization, he was hospitalized for angina pectoris like symptoms and myoedema; coronary angiography showed no coronary stenosis. Imiquimod was discontinued. Five days after admission, capillary leak syndrome was diagnosed. The reporter stated, “all observed reactions [hypotonia, tachycardia, rhabdomyolysis, increasing renal insufficiency, respiratory insufficiency, liver failure, intestinal failure, heart failure, lactacidosis, exhaustion reaction] seem to be caused by the capillary leak syndrome.” He was treated with cortisone, venesection, “adrenaline and volume,” **transfusion of five erythrocyte concentrates, and fresh plasma (questionable)** on unspecified dates. Thirty-one days after admission, the EKG was within normal limits. He was discharged after 38 days in the hospital. Medical history included high blood pressure and hair transplant; concomitant medications were not reported.

Table 2. Relevant laboratory values for ISR 4250028⁴

<u>Time after starting imiquimod</u>	<u>12 days</u> <u>(1st hospital</u> <u>admission)</u>	<u>13</u> <u>days</u>	<u>16</u> <u>days</u>	<u>20</u> <u>days</u>	<u>61</u> <u>days</u>	<u>77 days</u> <u>(2nd hospital</u> <u>admission)</u>	<u>92 days</u> <u>(3rd hospital</u> <u>admission)</u>	<u>168</u> <u>days</u>
Thrombocytes (150-350 x 10 ³ /mm ³)	221	124	82	174	257			
Leucocytes (4.5-11 x 10 ³ /mm ³)	19	14	6.1	7.2	4.3			
Erythrocytes (4.5-5.9 x 10 ⁶ /mm ³)	7.75					“anemia”		
Hemoglobin (13.5-17.5 g/dL)	23.7	12.7	8.1	9.6	12.2		20.6	13.6
Hematocrit (41%-53%)	68%						62%	40%

Reviewer Comment: Although the patient experienced low red blood cells / anemia, low white blood cells, and low platelets, as well as transfusions of red blood cells and plasma (questionable), these events were reported over the course of three hospitalizations. The three laboratory values relevant to pancytopenia (red blood cells, white blood cells, platelets) were not decreased at the same time during any of his hospitalizations. However, given that these cells turnover at varying rates and may have different effects over time, the findings from this case do not preclude the suppressive effects imiquimod may have on bone marrow elements.

3.1.2 LYMPHOMA

Table 3 provides a summary of the eight cases in which lymphoma was reported with imiquimod use.

Table 3. Characteristics of cases of lymphoma reported with imiquimod from marketing to June 24, 2009 (n=8)				
Origin	US (6)	Foreign (2)		
Gender	Male (4)	Female (4)		
Report type	Expedited (6)	Direct (2)		
FDA received date	2000 (1) 2006 (1)	2003 (1) 2007 (2)	2004 (1) 2008 (1)	2005 (1)
Age (n=7)	Mean: 61 years	Median: 60 years	Range: 26 – 83 years	
Time to lymphoma from initiation of treatment (n=4)	5 days (1)	6 weeks (1)	~6 months (1)	~3.25 years (1)
Imiquimod dosing	Daily (3)	2x/week (2)	Unknown (3)	
Indications	Labeled: AK (1), Viral warts (1), sBCC (1) Other: BCC (1), Cancerous and precancerous basal cells (1), Lymphoma (1), Malignant melanoma (1), Unknown (1)			
Lymphoma adverse event terms	Lymphoma (4) Non-Hodgkin's lymphoma (2) Mantle cell lymphoma (1) Lymphocytic infiltration + lymphoproliferative disorder (1)			
Diagnostic testing for lymphoma (n=5)	Post-mortem (1) Biopsy, CT scan, PET scan, ultrasound, neck dissection (1) Biopsy, flow cytometry (1) CT scan (1) Histopathology (1)			
Treatment required (n=5)	Excision (2)	Unspecified chemotherapy (2)	Neck dissection (1)	
Primary Outcome	Death (1)	Life-threatening (2)	Required Intervention (1)	Other (4)
Confounded cases (n=2)	Medical history included "other lymphoma" (1) Used to treat lymphoma (1)			

3.1.3 CARDIOVASCULAR EVENTS

Table 4 provides a summary of the 15 cases in which cardiovascular events of interest were reported with imiquimod use.

Table 4. Characteristics of cases of cardiovascular events of interest reported with imiquimod from marketing to June 24, 2009 (n=15)				
Origin	US (12)	Foreign (3)		
Gender	Male (9)	Female (6)		
Report type	Expedited (14)	Periodic (1)		
FDA received date	2001 (1) 2005 (4)	2002 (1) 2006 (2)	2003 (1) 2007 (1)	2004 (3) 2009 (2)
Age	Mean: 72 years	Median: 77 years	Range: 40–98 years	
Time to cardiovascular event from initiation of treatment (n=9)	Mean: 25 days	Median: 14 days	Range: 5 days – 4 months	
Imiquimod dosing	2x/day (1) Unknown (1)	Daily (3)	5x/week (2)	3x/week (7) 2x/week (1)
Indications	Labeled: AK (5), AK + sBCC (1) Other: BCC (4), Flat warts on hand (1), Warts and skin dysplasia (1), Melanoma (2), Metastasis of melanoma (1)			
Cardiovascular event	Stroke (6) Thrombosis (1) Elevated creatinine phosphokinase (1)	Arrhythmia (3) Pulmonary thrombus (1)	Myocardial infarction (2) Peripheral embolism (1)	
Primary Outcome	Death (5)	Hospitalization (6)	Life-threatening (2)	Other (2)
Confounded cases* (n=8)	Hypertension, or medications to treat hypertension (6) High cholesterol, or medication to treat high cholesterol (4) Concomitant use of clopidogrel (2) Diabetes, or medication to treat diabetes (1) History of transient ischemic attacks (1) History of atrial fibrillation (1) History of stokes/mini-strokes, pace-maker and on unspecified heart medications and an unspecified blood thinner (1)			

* More than one is possible per case

A representative case is summarized below. The remaining cases are line listed in Appendix D.

ISR 4991080, US (2006): A 44 year old male used one sachet of imiquimod three times a week for 13 days to treat BCC on his forehead. Eight days after starting imiquimod (the last dose was the night before), he was taken to the emergency room where he experienced palpitations and *supraventricular tachycardia* (150 beats/minute); his blood pressure was 133/100. The EKG and “complete blood work-up including thyroid tests” were normal. He was discharged with a portable cardiac monitor. He did not use imiquimod for the next 3 days; on the fourth day after discharge, he used imiquimod. The following day, he was taken to the emergency room again due to palpitations, *supraventricular tachycardia*, and an increase in blood pressure. The EKG and “complete blood work-up including thyroid tests” were normal and he was discharged. Imiquimod was discontinued and at the time of reporting, he had not experienced any further symptoms. Concomitant medications were not reported; however, the patient reports being “healthy without pre-existing medical conditions,” does not drink or smoke, and is not overweight.

3.2 DATA MINING

Appendix E lists EBGM values and confidence limits for various MedDRA preferred terms associated with imiquimod in the AERS data and relevant to this review (see Sections 2.1.1-2.1.3). There were no EBGM scores greater than 2. The highest association score (EBGM = 1.47) is for the imiquimod-lymphoma drug-event combination; however, this value is less than 2 (i.e. lymphoma was reported 1.47 times more frequently with imiquimod in the AERS database than the expected rate considering all other drugs and events in AERS). The highest EB05 (EB05 = 0.64) is also for lymphoma, and is less than 1 (i.e. the lower limit of the 95% confidence interval for lymphoma and imiquimod is less than the expected rate considering all other drugs and events in AERS).

In this analysis, EBGM values indicate the strength of the reporting relationship between a particular drug and event. For example, if EBGM=10 for a drug-event combination, then the drug-event was reported 10 times more frequently in the AERS database than statistically expected when considering all other drugs and events in AERS database as a background “expected.” A drug-event combination having an EB05 ≥ 2 indicates 95% confidence that this drug-event combination is reported at least at twice the expected rate when considering all other drugs and events in the database. A drug-event combination having an EB05 > 1 indicates 95% confidence that this drug-event combination occurs at least at a higher-than-expected rate considering all other drugs and events in the database.

In this analysis, the higher the EBGM score (and accompanying EB05, EB95 confidence intervals) for a particular drug-event, the higher the association between that drug and event, given the database being analyzed. Note that this “association” is a result of the relative reporting for various events among all drugs in the database. The scores discussed in this section provide an indication of the association of pancytopenia, lymphoma, and cardiovascular events or interest with imiquimod, given the data analyzed. The exact degree of this association (in all patients exposed to the drug worldwide), however, cannot be elicited from an MGPS data mining analysis alone, because the association scores (EBGM values) from such an analysis are generated from the specific database analyzed—in this case AERS which consists of spontaneous adverse events reports. It is also important to understand that an elevated EBGM score of association for a particular drug-event combination does not prove causality or an increased relative risk of that drug-event. Similarly, the absence of an elevated EBGM score for a drug-event cannot be interpreted as a definite lack of association for that drug-event. Finally, reporting and detection biases can occur in AERS and effects of concomitant illnesses or therapy cannot be fully controlled in data mining analyses using MGPS. Because of the spontaneous nature of reporting, the results of this analysis should not be interpreted as a formal comparison of treatment groups or of their relative risks.

4 DISCUSSION

Imiquimod is an immune response modifier for topical administration. The mechanism of action of imiquimod is unknown; however, the label states that imiquimod does not have any direct antiviral activity in cell culture. Although the clinical relevance is unknown, a study in subjects with genital/perianal warts (n=22) showed that imiquimod induced mRNA encoding cytokines

(including interferon- α) at the treatment site and decreased human papillomavirus (HPV) DNA and HPV-L1 mRNA. Studies in patients with AK (n=18) and sBCC (n=6) showed that imiquimod increased CD3, CD4, CD8, CD11a, and CD68 (AK study) and may also increase infiltration of lymphocytes, dendritic cells, and macrophages (sBCC study); however the clinical relevance is unknown.¹

Although the mechanism of action for imiquimod is not completely understood, imiquimod stimulates the production and secretion of pro-inflammatory cytokines including interferon alpha (IFN- α), tumor necrosis factor alpha (TNF- α), interleukin (IL)-2, IL-6, IL-8, and IL-12. While it is unclear whether these effects are local or systemic, the potential may exist for imiquimod to be associated with medical conditions affected by pro-inflammatory cytokines including myocardial infarction and atherosclerotic disease.⁵⁻⁷

Systemic absorption was seen in 58 subjects with AK who used imiquimod three times a week for 16 weeks; mean peak serum concentrations at the end of week 16 were 0.1 ng/mL (face, 12.5 mg imiquimod), 0.2 ng/mL (scalp, 25 mg imiquimod), and 3.5 ng/mL (hands/arms, 75 mg imiquimod). From this study, it appeared that systemic absorption might be more dependent on the surface area of application than the amount of dose applied. Systemic absorption was also seen in 12 subjects with genital/perianal warts who used an average dose of 4.6 mg of imiquimod; the mean peak serum concentration was 0.4 ng/mL in these subjects. Additionally, topical overdoses may increase the risk for systemic adverse events.¹ However, it is unclear if serum concentrations of imiquimod correlate directly with adverse events.

Although the relationships between pro-inflammatory cytokines and systemic absorption of imiquimod with the adverse events analyzed in this review are not known, the potential for an association cannot be excluded.

4.1.1 PANCYTOPENIA

We identified one case in the pancytopenia search that resulted in hospitalization. This case occurred in a 56 year old male who used imiquimod three times a week to treat AK. The patient experienced low red blood cells / anemia, low white blood cells, and low platelets, as well as transfusions of red blood cells and plasma (questionable) that occurred over the course of three hospitalizations. However, given that these cells turnover at varying rates and may have different effects over time, the findings from this case do not preclude the suppressive effects imiquimod may have on bone marrow elements. This case is not suggestive of imiquimod-induced pancytopenia since all three laboratory values relevant to pancytopenia (red blood cells, white blood cells, platelets) were not decreased at the same time during any of his hospitalizations. Additionally, the report states that the patient underwent multiple venesections and was eventually diagnosed with capillary leak syndrome.

4.1.2 LYMPHOMA

We identified eight cases of adverse events related to lymphoma with serious outcomes in AERS, including one literature case and one study case. One case occurred in a patient with a failing renal transplant; this case was also confounded due to a medical history of “other

lymphoma.” Another case was confounded due to the use of imiquimod to treat lymphoma. Four cases reported the time from the start of imiquimod therapy to the onset of the lymphoma related event (5 days, 6 weeks, ~6 months, and ~3.25 years). However, malignancies may be associated with a time lag making it difficult to attribute the adverse event to a drug, particularly in cases reporting a relatively short time to event onset. Additionally, dechallenge and rechallenge information is difficult to determine in this situation due to the delayed time to event and need for medical intervention associated with malignancies.

Imiquimod was discontinued in four cases (one day before the event-1, the day of the event-1, an unknown amount of time the event-2). Three of these four cases required intervention (excision-1, neck dissection-1, unspecified chemotherapy-1); the events resolved in one case and the eventual clinical outcome was unknown in the other two cases. The fourth case reporting discontinuation of imiquimod did not report the eventual clinical outcome. Imiquimod therapy was continued in one case and the adverse events resolved following treatment with unspecified chemotherapy. The action taken regarding imiquimod was unknown in the remaining three cases; one of these cases resulted in death likely due to a failing renal transplant, one case reported resolution of the events following excision, and one case reported the events as ongoing.

Five cases reported diagnostic test results including biopsy, imaging scans, and post-mortem results supporting the diagnosis (lymphoma-2, non-Hodgkin’s lymphoma-2, lymphocytic infiltration + lymphoproliferative disorder-1); the remaining three cases (lymphoma-2, mantle cell lymphoma-1) did not report diagnostic test results.

4.1.3 CARDIOVASCULAR EVENTS

We identified 15 cases of adverse events related to ischemic heart disease, thromboembolic events, and arrhythmias with serious outcomes in AERS. Nine cases reported the time from the start of imiquimod therapy to the cardiovascular event with a range of 5 days to 4 months and median of 14 days; however, the event occurred 2-10 days after imiquimod therapy was stopped in three cases.

Stroke (n=6)

Six cases of stroke were reported in patients 63 to 81 years of age. All six cases resulted in hospitalization and subsequent resolution (i.e. all patients were discharged); however, in one case the patient died 26 days later from an unknown cause. Imiquimod was discontinued prior to the stroke in two cases (2 days prior, 5 days prior). In another case, imiquimod was discontinued; however, the temporal relationship to the stroke was unknown. Imiquimod therapy was continued in two cases. The action regarding imiquimod was unknown in the remaining case. All six cases of stroke occurred in elderly patients and were confounded due to one or more of the following medical conditions (high cholesterol-1, hypertension-4, atrial fibrillation-1, transient ischemic attacks-1, stroke/mini-strokes-1) and/or the use of one or more of the following concomitant medications associated with risk factors (cholesterol lowering agent-3, anti-hypertensive-2, clopidogrel-1, unspecified heart medication-1, unspecified blood thinner-1).

Arrhythmia (n=3)

Three cases of arrhythmia were reported in patients 40, 44, and 98 years of age resulting in death (1) or other serious outcome (2). There were no reports of QT prolongation or Torsades de Pointes. The 98 year old died 17 days after imiquimod was discontinued due to an unspecified hepatic disorder; a cardiac arrhythmia was reported on an unknown date. The 44 year old experienced a positive rechallenge of supraventricular tachycardia and reported that the event did not recur after imiquimod was discontinued the second time. The 40 year old reported discontinuing imiquimod; however, the eventual clinical outcome was unknown. None of these cases reported confounding medical histories or concomitant medications.

Myocardial infarction (n=2)

Two cases of life-threatening myocardial infarctions were reported in patients 59 and 77 years of age. Imiquimod was discontinued in the 77 year old who required hospitalization; the eventual clinical outcome is unknown. This case was confounded by the concomitant use of medications associated with risk factors for coronary heart disease including metformin, verapamil, ezetimibe, telmisartan, clopidogrel, and “ceschol.” The action taken regarding imiquimod is unknown in the 59 year old; however, the patient did not report any problems in the 20 months following the myocardial infarction. This case did not report concomitant medications or medical history.

Other cardiovascular events of interest (n=4)

Four cases of other cardiovascular events of interest were reported in patients 68 to 80 years of age including pulmonary thrombus (1), thrombosis (1), peripheral embolism (1), and elevated creatinine phosphokinase (1). Two cases resulted in death following a thromboembolic event within three months of starting imiquimod. One additional case reported death from an unknown cause. The remaining case reported hospitalization and a positive rechallenge of elevated creatinine phosphokinase; the patient recovered after imiquimod was discontinued the second time. All four cases occurred in elderly patients; the case reporting death due to embolism in particular, reported a significant past medical history of a renal transplant 25 years prior (after which she experienced arteriopathy), non-functioning A-V fistula in right arm, squamous cell carcinoma, and high cholesterol. The case of elevated creatinine phosphokinase reported that the patient was on “many” unspecified medications and had a medical history. The remaining two cases did not report any significant concomitant medications or medical history.

5 CONCLUSIONS

Although one AERS case was identified in the pancytopenia search, review of the case does not suggest a compelling post-marketing safety signal for pancytopenia.

The latency period between drug exposure and occurrence of malignancies (including lymphoma) combined with the limitations associated with post-marketing adverse event reports, makes it difficult to draw conclusions regarding this adverse event. Although an association

between imiquimod and lymphoma cannot be ruled out, the AERS cases do not suggest a compelling post-marketing safety signal for lymphoma.

Based on the AERS cases of arrhythmia, including one case describing a positive rechallenge of a supraventricular tachycardia, it is possible that imiquimod is associated with a risk of arrhythmia. Although an association between imiquimod and the remaining cardiovascular events of interest (i.e. ischemic heart disease and thromboembolic events) cannot be ruled out, the AERS cases are not compelling and do not support a post-marketing signal for these events.

6 RECOMMENDATIONS

Since this review did not identify any new post-marketing safety signals, DPV has no recommendations for labeling enhancements at this time.

7 REFERENCES

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8 APPENDICES

Appendix A. Pancytopenia AERS search strategy

Appendix B. Cardiovascular AERS search strategy

Appendix C. Line listing for cases of lymphoma reported with imiquimod from marketing to June 24, 2008 (n=8)

Appendix D. Line listing for cases of ishchemic heart disease, thromboembolic events, and arrhythmias reported with imiquimod from marketing to June 24, 2008 (n=15)

Appendix E. Data mining results for preferred terms related to this review, sorted by descending EB05 value

8.1 APPENDIX A. PANCYTOPENIA AERS SEARCH STRATEGY

Cytopenia and haematopoietic disorders affecting more than one type of blood cell SMQ (broad search) includes the following preferred terms:

- Aplastic anaemia
- Aspiration bone marrow abnormal
- Bicytopenia
- Biopsy bone marrow abnormal
- Blood count abnormal
- Blood disorder
- Bone marrow disorder
- Bone marrow failure
- Bone marrow myelogram abnormal
- Bone marrow necrosis
- Bone marrow toxicity
- Congenital aplastic anaemia
- Febrile bone marrow aplasia
- Full blood count decreased
- Haematotoxicity
- Myelodysplastic syndrome
- Myelodysplastic syndrome transformation
- Pancytopenia
- Panmyelopathy
- Plasmablast count decreased
- Scan bone marrow abnormal

8.2 APPENDIX B. CARDIOVASCULAR AERS SEARCH STRATEGY

Ischaemic heart disease SMQ (broad search) includes the following preferred terms:

- Acute coronary syndrome
- Acute myocardial infarction
- Angina pectoris
- Angina unstable
- Arteriogram coronary abnormal
- Arteriosclerosis coronary artery
- Arteriospasm coronary
- Blood creatine phosphokinase abnormal
- Blood creatine phosphokinase increased
- Blood creatine phosphokinase MB abnormal
- Blood creatine phosphokinase MB increased
- Cardiac enzymes increased
- Computerized tomogram coronary artery abnormal
- Coronary angioplasty
- Coronary arterial stent insertion
- Coronary artery bypass
- Coronary artery disease
- Coronary artery dissection
- Coronary artery embolism
- Coronary artery insufficiency
- Coronary artery occlusion
- Coronary artery reocclusion
- Coronary artery restenosis
- Coronary artery stenosis
- Coronary artery thrombosis
- Coronary bypass thrombosis
- Coronary endarterectomy
- Coronary no-reflow phenomenon
- Coronary ostial stenosis
- Coronary revascularization
- Dissection coronary artery aneurysm
- ECG signs of myocardial ischaemia
- Electrocardiogram Q wave abnormal
- Electrocardiogram ST segment abnormal
- Electrocardiogram ST segment depression
- Electrocardiogram ST segment elevation
- Electrocardiogram ST-T segment abnormal
- Electrocardiogram ST-T segment depression
- Electrocardiogram ST-T segment elevation
- Exercise electrocardiogram abnormal
- Exercise test abnormal
- External counterpulsation
- Haemorrhage coronary artery
- Infarction
- In-stent coronary artery restenosis
- Ischaemic cardiomyopathy
- Microvascular angina
- Myocardial infarction
- Myocardial ischaemia
- Myocardial reperfusion injury
- Papillary muscle infarction
- Percutaneous coronary intervention
- Post procedural myocardial infarction
- Postinfarction angina
- Prinzmetal angina
- Scan myocardial perfusion abnormal
- Silent myocardial infarction
- Stress cardiomyopathy
- Subclavian coronary steal syndrome
- Subendocardial ischaemia
- Troponin I increased
- Troponin increased
- Troponin T increased
- Vascular graft occlusion

Torsade de pointes / QT prolongation SMQ (broad search) includes the following preferred terms:

- Cardiac arrest
- Cardiac death
- Cardio-respiratory arrest
- Electrocardiogram QT interval abnormal
- Electrocardiogram QT prolonged
- Electrocardiogram repolarisation abnormality
- Electrocardiogram U-wave abnormality
- Electrocardiogram U-wave biphasic
- Long QT syndrome
- Long QT syndrome congenital
- Loss of consciousness
- Sudden cardiac death
- Sudden death
- Syncope
- Syncope vasovagal
- Torsades de pointes
- Ventricular arrhythmia
- Ventricular fibrillation
- Ventricular flutter
- Ventricular tachyarrhythmia
- Ventricular tachycardia

Embolic and thrombotic events SMO (broad search) includes the following preferred terms:

- Acute myocardial infarction
- Amaurosis
- Amaurosis fugax
- Angiogram abnormal
- Angiogram cerebral abnormal
- Angiogram peripheral abnormal
- Angioplasty
- Aortic bypass
- Aortic embolus
- Aortic surgery
- Aortic thrombosis
- Aortogram abnormal
- Arterectomy with graft replacement
- Arterial bypass operation
- Arterial graft
- Arterial occlusive disease
- Arterial stent insertion
- Arterial therapeutic procedure
- Arterial thrombosis
- Arterial thrombosis limb
- Arteriogram abnormal
- Arteriogram carotid abnormal
- Arteriovenous fistula occlusion
- Arteriovenous fistula thrombosis
- Arteriovenous graft thrombosis
- Atherectomy
- Atrial thrombosis
- Axillary vein thrombosis
- Basilar artery occlusion
- Basilar artery thrombosis
- Blindness transient
- Bone infarction
- Brain stem infarction
- Brain stem stroke
- Brain stem thrombosis
- Budd-Chiari syndrome
- Capsular warning syndrome
- Carotid arterial embolus
- Carotid artery bypass
- Carotid artery occlusion
- Carotid artery stent insertion
- Carotid artery thrombosis
- Carotid endarterectomy
- Catheter related complication
- Catheter thrombosis
- Catheterisation venous
- Embolism venous
- Endarterectomy
- Femoral artery embolism
- Femoral artery occlusion
- Foetal cerebrovascular disorder
- Graft thrombosis
- Haemorrhagic cerebral infarction
- Haemorrhagic infarction
- Haemorrhagic stroke
- Haemorrhagic transformation stroke
- Hemiparesis
- Hemiplegia
- Hepatic artery embolism
- Hepatic artery occlusion
- Hepatic artery thrombosis
- Hepatic infarction
- Hepatic vein occlusion
- Hepatic vein thrombosis
- Hypothenar hammer syndrome
- Iliac artery embolism
- Iliac artery occlusion
- Iliac artery thrombosis
- Iliac vein occlusion
- Implant site thrombosis
- Infarction
- Inferior vena caval occlusion
- Infusion site thrombosis
- Injection site thrombosis
- Intestinal infarction
- Intra-aortic balloon placement
- Intracardiac mass
- Intracardiac thrombus
- Intracranial venous sinus thrombosis
- Intraoperative cerebral artery occlusion
- Intravenous catheter management
- Ischaemic cerebral infarction
- Ischaemic stroke
- Jugular vein thrombosis
- Lacunar infarction
- Mesenteric arteriosclerosis
- Mesenteric artery embolism
- Mesenteric artery stenosis
- Mesenteric artery thrombosis
- Mesenteric occlusion
- Mesenteric vascular insufficiency
- Mesenteric vein thrombosis
- Pulmonary venous thrombosis
- Quadripareisis
- Quadriplegia
- Renal artery occlusion
- Renal artery thrombosis
- Renal embolism
- Renal infarct
- Renal vein embolism
- Renal vein occlusion
- Renal vein thrombosis
- Retinal artery embolism
- Retinal artery occlusion
- Retinal artery thrombosis
- Retinal infarction
- Retinal vascular thrombosis
- Retinal vein occlusion
- Retinal vein thrombosis
- Shunt occlusion
- Shunt thrombosis
- SI QIII TIII pattern
- Silent myocardial infarction
- Spinal artery embolism
- Spinal cord infarction
- Splenic embolism
- Splenic infarction
- Splenic vein occlusion
- Splenic vein thrombosis
- Stent embolisation
- Stent occlusion
- Stress cardiomyopathy
- Stroke in evolution
- Subclavian artery embolism
- Subclavian artery thrombosis
- Subclavian vein thrombosis
- Superior mesenteric artery syndrome
- Superior sagittal sinus thrombosis
- Superior vena caval occlusion
- Surgical vascular shunt
- Testicular infarction
- Thalamic infarction
- Thrombectomy
- Thromboangiitis obliterans
- Thromboembolectomy
- Thrombolysis
- Thrombophlebitis
- Thrombophlebitis migrans

- Cavernous sinus thrombosis
- Central venous catheterisation
- Cerebellar artery occlusion
- Cerebellar artery thrombosis
- Cerebellar embolism
- Cerebellar infarction
- Cerebral artery embolism
- Cerebral artery occlusion
- Cerebral artery thrombosis
- Cerebral hypoperfusion
- Cerebral infarction

- Cerebral infarction foetal
- Cerebral ischaemia
- Cerebral thrombosis
- Cerebral venous thrombosis
- Cerebrospinal thrombotic tamponade
- Cerebrovascular accident

- Cerebrovascular accident prophylaxis
- Cerebrovascular disorder
- Cerebrovascular insufficiency
- Cerebrovascular operation
- Cerebrovascular stenosis
- Choroidal infarction
- Compression stockings application
- Coronary angioplasty
- Coronary arterial stent insertion
- Coronary artery bypass
- Coronary artery embolism
- Coronary artery occlusion

- Coronary artery reocclusion

- Coronary artery thrombosis
- Coronary bypass thrombosis
- Coronary endarterectomy
- Coronary revascularisation
- Deep vein thrombosis
- Deep vein thrombosis postoperative
- Diplegia
- Directional Doppler flow tests abnormal
- Disseminated intravascular coagulation
- Disseminated intravascular coagulation in newborn
- Embolia cutis medicamentosa
- Embolic cerebral infarction
- Embolic pneumonia
- Embolic stroke
- Embolism

- Monoparesis
- Monoplegia
- Myocardial infarction
- Obstetrical pulmonary embolism
- Optic nerve infarction
- Paget-Schroetter syndrome
- Pancreatic infarction
- Papillary muscle infarction
- Paradoxical embolism
- Paraparesis
- Paraplegia

- Paresis
- Pelvic venous thrombosis
- Penile artery occlusion
- Penile vein thrombosis
- Percutaneous coronary intervention

- Peripheral arterial occlusive disease
- Peripheral artery angioplasty

- Peripheral embolism
- Peripheral revascularisation
- Phlebectomy
- Phleboplasty
- Pituitary infarction
- Placental infarction
- Pneumatic compression therapy
- Portal shunt
- Portal vein occlusion
- Portal vein thrombosis
- Post procedural myocardial infarction
- Post procedural pulmonary embolism
- Post procedural stroke
- Post thrombotic syndrome
- Postinfarction angina
- Postoperative thrombosis
- Postpartum venous thrombosis
- Precerebral artery occlusion

- Prosthetic vessel implantation
- Pulmonary artery therapeutic procedure
- Pulmonary artery thrombosis

- Pulmonary embolism

- Pulmonary infarction
- Pulmonary microemboli
- Pulmonary thrombosis
- Pulmonary vein occlusion
- Pulmonary veno-occlusive disease

- Thrombophlebitis neonatal
- Thrombosed varicose vein
- Thrombosis
- Thrombosis corpora cavernosa
- Thrombosis in device
- Thrombosis mesenteric vessel
- Thrombosis prophylaxis
- Thrombotic cerebral infarction
- Thrombotic microangiopathy
- Thrombotic stroke
- Thrombotic thrombocytopenic purpura
- Thyroid infarction
- Transient ischaemic attack
- Transverse sinus thrombosis
- Truncus coeliacus thrombosis
- Tumour embolism

- Tumour thrombosis

- Ultrasonic angiogram abnormal

- Ultrasound Doppler abnormal
- Vascular graft
- Vascular operation
- Vascular stent insertion
- Vasodilation procedure
- Vena cava embolism
- Vena cava filter insertion
- Vena cava thrombosis
- Venipuncture site thrombosis
- Venogram abnormal
- Venooclusive disease

- Venooclusive liver disease

- Venous occlusion
- Venous operation
- Venous recanalisation
- Venous stent insertion
- Venous thrombosis
- Venous thrombosis in pregnancy

- Venous thrombosis limb
- Venous thrombosis neonatal

- Vertebral artery occlusion

- Vertebral artery thrombosis

- Visual acuity reduced transiently
- Visual midline shift syndrome
- White clot syndrome

Cardiac arrhythmias SMQ (broad search) includes the following preferred terms:

- Accelerated idioventricular rhythm
- Accessory cardiac pathway
- Adams-Stokes syndrome
- Agonal rhythm
- Anomalous atrioventricular excitation
- Arrhythmia
- Arrhythmia neonatal
- Arrhythmia supraventricular
- Arrhythmogenic right ventricular dysplasia
- Atrial conduction time prolongation
- Atrial fibrillation
- Atrial flutter
- Atrial tachycardia
- Atrioventricular block
- Atrioventricular block complete
- Atrioventricular block first degree
- Atrioventricular block second degree
- Atrioventricular conduction time shortened
- Atrioventricular extrasystoles
- AV dissociation
- Bifascicular block
- Bradyarrhythmia
- Bradycardia
- Bradycardia foetal
- Bradycardia neonatal
- Brugada syndrome
- Bundle branch block
- Bundle branch block bilateral
- Bundle branch block left
- Bundle branch block right
- Cardiac arrest
- Cardiac arrest neonatal
- Cardiac death
- Cardiac fibrillation
- Cardiac flutter
- Cardiac telemetry abnormal
- Cardio-respiratory arrest
- Cardio-respiratory arrest neonatal
- Chronotropic incompetence
- Conduction disorder
- ECG P wave inverted
- Electrocardiogram abnormal
- Electrocardiogram ambulatory abnormal
- Electrocardiogram change
- Electrocardiogram delta waves abnormal
- Electrocardiogram P wave abnormal
- Electrocardiogram PQ interval prolonged
- Electrocardiogram PR prolongation
- Electrocardiogram PR shortened
- Electrocardiogram QRS complex prolonged
- Electrocardiogram QT prolonged
- Electrocardiogram repolarisation abnormality
- Electrocardiogram RR interval prolonged
- Electrocardiogram U-wave abnormality
- Electrocardiogram U-wave biphasic
- Electromechanical dissociation
- Extrasystoles
- Foetal arrhythmia
- Foetal heart rate deceleration
- Foetal heart rate disorder
- Gallop rhythm present
- Heart alternation
- Heart block congenital
- Heart rate abnormal
- Heart rate decreased
- Heart rate increased
- Heart rate irregular
- Long QT syndrome
- Long QT syndrome congenital
- Loss of consciousness
- Lown-Ganong-Levine syndrome
- Neonatal tachycardia
- Nodal arrhythmia
- Nodal rhythm
- Pacemaker generated arrhythmia
- Palpitations
- Parasystole
- Paroxysmal arrhythmia
- Reperfusion arrhythmia
- Rhythm idioventricular
- Sick sinus syndrome
- Sinoatrial block
- Sinus arrest
- Sinus arrhythmia
- Sinus bradycardia
- Sinus tachycardia
- Sudden cardiac death
- Sudden death
- Supraventricular extrasystoles
- Supraventricular tachyarrhythmia
- Supraventricular tachycardia
- Syncope
- Syncope vasovagal
- Tachyarrhythmia
- Tachycardia
- Tachycardia foetal
- Tachycardia paroxysmal
- Torsade de pointes
- Trifascicular block
- Ventricular arrhythmia
- Ventricular asystole
- Ventricular extrasystoles
- Ventricular fibrillation
- Ventricular flutter
- Ventricular pre-excitation
- Ventricular tachyarrhythmia
- Ventricular tachycardia
- Wandering pacemaker
- Withdrawal arrhythmia
- Wolff-Parkinson-White syndrome
- Wolff-Parkinson-White syndrome congenital

8.3 APPENDIX C. LINE LISTING FOR CASES OF LYMPHOMA REPORTED WITH IMIQUIMOD FROM MARKETING TO JUNE 24, 2008 (N=8)

ISR#	Source, Type (FDA Received date)	Age (years), Gender	Outcome	Imiquimod dosing and indication	Summary and Comments
3517287	Foreign, E (2000)	26, F	Death	NS, viral warts	Patient with chronic renal failure and a failing transplant developed gastrointestinal bleeding, disseminated intravascular coagulation, and hepatic failure after a 2 nd transplant; she died 2 weeks later. She was treated with imiquimod (dates unknown). Post-mortem revealed <i>infiltrating lymphoma of liver</i> . Concomitant medications include prednisolone, cyclosporine, and azathioprine; medical history included “other lymphoma.”
5983113	US, D (2008)	60, M	Life-threatening	0.25 grams used 2x/week for ~6 months, AK	Patient was diagnosed with <i>non-Hodgkin’s large B cell lymphoma</i> (as per CT scan) ~6 months after starting imiquimod. Imiquimod was discontinued and he was treated with unspecified chemotherapy. Concomitant medications and medical history were not reported.
5206971	US, D (2007)	74, M	Life-threatening	Used daily for ~6 months, cancerous and precancerous basal cells on head and neck	An unspecified time after starting imiquimod, an <i>enlarged left neck lymph node</i> was noted which was diagnosed as a <i>squamous cell malignancy</i> (as per biopsy, CT scan, PET scan, ultrasound, and neck dissection). Patient required surgery (neck dissection) ~7 weeks after imiquimod was discontinued. Medical history included removal of numerous BCC over past 30 years; concomitant medications were not reported.
4674381	US, E (2005)	60, M	Required Intervention	Used 2x/week for ~3.25 years, malignant melanoma on scalp	Patient experienced <i>mantle cell lymphoma on his lungs</i> ~3.25 years after starting imiquimod (therapy details unknown) and was treated with unspecified chemotherapy. He was in remission at the time of reporting and imiquimod therapy was ongoing. Concomitant medications and medical history were not reported.
5244004	US, E (2007)	NS, F	Other	NS, NS	Patient developed <i>lymphoma</i> an unspecified amount of time after starting imiquimod (therapy details unknown); events were reported as ongoing. Concomitant medications and medical history were not reported.
5148785	US, E (2006) Literature	74, F	Other	Used for 6 weeks, BCC	The area treated with imiquimod became inflamed/ulcerated and was excised (date unknown). Patient experienced an <i>atypical lymphocytic reaction with epidermotropism and a lymphocytic vasculopathic reaction</i> (as per histopathology). She was asymptomatic 7 months later (follow-up visit). Concomitant medications and medical history not reported.
4389856	US, E (2004)	50, M	Other	0.5 sachet used daily for 5 days, “lymphoma”	After 5 days of imiquimod therapy, patient noticed the <i>nodule was “growing and ulcerating”</i> and imiquimod therapy was stopped; it is unknown if the events resolved. There were no concomitant medications; medical history was not reported.

4251137	US, E (2003) Study	83, F	Other	Used daily for 6 weeks, sBCC on back	The day after the last application of imiquimod, subject reported a “recently” noticed palpable neck lymph node which remained unchanged 4 weeks post-treatment. Additional lymph nodes were noticed 12 weeks post-treatment and a right neck mass and supraclavicular mass were excised ~18 days later. Biopsy results showed follicular lymphoma grade two and flow cytometry showed B-cells positive for CD20; subsequently, <u><i>non-Hodgkin’s lymphoma</i></u> was diagnosed. The oncologist noted one palpable right neck lymph node ~8 months later; no treatment was advised and she remained asymptomatic ~2 years after the excision. There was no relevant medical history or concomitant medications.
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Abbreviations: NS=Not stated, E=Expedited (15-day), D=Direct, sBCC=Superficial basal cell carcinoma, BCC=Basal cell carcinoma, AK=Actinic keratosis,

8.4 APPENDIX D. LINE LISTING FOR CASES OF ISHCHEMIC HEART DISEASE, THROMBOEMBOLIC EVENTS, AND ARRHYTHMIAS REPORTED WITH IMIQUIMOD FROM MARKETING TO JUNE 24, 2008 (N=15)

Arrhythmia (n=3)

ISR#	Source, Type (FDA Received date)	Age (years), Gender	Outcome	Imiquimod dosing and indication	Summary and Comments
4250509	France, E (2003)	98, M	Death	Used 2x/day for 26 days, BCC on “skull”	Patient hospitalized with hemolytic anemia 10 days after discontinuing imiquimod; he died of an unspecified hepatic disorder 7 days later. An EKG (date unknown) showed an <u>arrhythmia</u> . Medical history included cholecystectomy; no concomitant medications.
4991080	US, E (2006)	44, M	Other	1 sachet used 3x/week for 13 days, BCC on forehead	Patient went to the ER 8 days after starting imiquimod (last dose was the night before) where he experienced palpitations, <u>SVT</u> , and high blood pressure. The EKG blood work-up was normal. He was discharged with a portable cardiac monitor and did not use imiquimod for the next 3 days. On the 4 th day, he used imiquimod and was taken to the ER the next day since the events recurred. Imiquimod was discontinued and he has not experienced any symptoms since. He has no relevant medical history; concomitant medications not reported.
5087974	US, E (2006)	40, F	Other	0.5 sachet used 3x/week (later increased to 5x/week), AK on nose	Patient applied imiquimod 3x/week for an unspecified amount of time, then increased the dose to 5x/week. Within 1 month of increasing the dose, she experienced flu-like symptoms, chest pain, severe leg cramps, and an enlarged lymph node; imiquimod was discontinued. The next day, a cardiac enzyme test (normal) and <u>EKG (abnormal)</u> were performed. A cardiac stress test was done the next day, but results were not reported. She was not on any concomitant medications and did not have any relevant medical history.

Myocardial infarction (n=2)

ISR#	Source, Type (FDA Received date)	Age (years), Gender	Outcome	Imiquimod dosing and indication	Summary and Comments
6175679	US, P (2009)	77, M	Life-threatening	Used 5x/week for 5 days, AK	Patient experienced <u>MI</u> 5 days after starting imiquimod and was hospitalized on an unspecified date. Imiquimod was discontinued. Concomitant medications include metformin, verapamil, ezetimibe, “ceschol,” telmisartan, and clopidogrel; medical history not reported.
4352283	US, E (2002)	59, F	Life-threatening	Used for ~3 months, BCC near left bicep	Patient experienced <u>MI</u> ~3 months after starting imiquimod. On an unspecified date, an angiogram showed her arteries were “clear.” It is unknown if imiquimod was discontinued. Follow-up reports that she is on an unspecified medication for her heart and has not experienced any problems since the MI. Concomitant medications and medical history were not reported.

Stroke (n=6)

ISR#	Source, Type (FDA Received date)	Age (years), Gender	Outcome	Imiquimod dosing and indication	Summary and Comments
4515426	US, E (2004) Study	80, F	Death	0.1 sachet daily for ~4 months, BCC on nose	Subject hospitalized due to bacteremia ~4 months after starting imiquimod; imiquimod was discontinued upon admission. Two days later, she experienced a <u>stroke</u> . She was discharged after 21 days in the hospital and died at home 26 days later (cause unknown). Concomitant medications include quinine, trazodone, tolterodine, infliximab, imipramine, omeprazole, stool softener, lisinopril, metoprolol, folic acid, aspirin, and a multivitamin; medical history included rheumatoid arthritis with spinal stenosis, mitral valve prolapse, kidney stone, breast reduction, and carpal tunnel surgery.
3762402	US, E (2001)	63, M	Hospitalization	0.75 sachet used 3x/week for 14 days, flat warts on hand	Patient hospitalized 13 days after starting imiquimod due to a <u>“mini-stroke.”</u> He recovered after an unspecified amount of time; treatment with imiquimod was continued. Concomitant medications include atorvastatin and tramadol; medical history was not reported.
4354988	US, E (2004)	80, M	Hospitalization	0.1 sachet used daily, AK on nose	Patient hospitalized 8 days after starting imiquimod due to a <u>TIA</u> . While hospitalized, arterial blockages were found in neck and an angioplasty scheduled. He was discharged 1 day after admission and treatment with imiquimod continued. Concomitant medications included valsartan, hydrochlorothiazide, lovastatin, timolol, and testosterone; medical history included glaucoma, hypertension, and high cholesterol.
4618646	US, E (2005)	79, F	Hospitalization	1 sachet used 3x/week for 10 days, AK on chest	Patient hospitalized 5 days after discontinuing imiquimod due to a <u>lacunar stroke of the basal ganglia</u> . Her blood pressure was 170/90 and INR was elevated. She was discharged an unspecified amount of time after the event. Concomitant medications include warfarin; medical history included hypertension and atrial fibrillation.
4684551	US, E (2005)	77, M	Hospitalization	0.1 sachet used daily, melanoma in situ on left ear	Patient was hospitalized 23 days after starting imiquimod due to a <u>left lacunar infarction</u> (as per brain CT scan, carotid ultrasound was normal). He was discharged 2 days after admission; the action taken regarding imiquimod was unknown. Concomitant medications include clopidogrel, pantoprazole, calcipotriene, acetylsalicylic acid, and multivitamins; medical history included GERD, hypertension, constipation, osteoarthritis, TIA, psoriasis, BCC, diverticulosis, and allergies to penicillin and meperidine.
6050381	US, E (2009)	81, M	Hospitalization	Used 2x/week, melanoma on scalp	Patient hospitalized an unspecified amount of time after starting imiquimod due to a <u>stroke</u> , “bleeding on the brain,” and brain swelling (as per CT scan). He was discharged and imiquimod discontinued on unspecified dates. Concomitant medications include a heart medication, a blood thinner, and metoprolol; medical history included a pacemaker, forehead sun damage, freezing off lesions, stroke, and 30 mini-strokes in 10 years (as per CT scan).

Other cardiovascular events of interest (n=4)

ISR#	Source, Type (FDA Received date)	Age (years), Gender	Outcome	Imiquimod dosing and indication	Summary and Comments
5623827	US, E (2007)	77, M	Death	Used 5x/week, sBCC and AK on face and chest	The patient experienced local skin reactions an unspecified amount of time after starting imiquimod; imiquimod was discontinued and doxycycline prescribed. Three days after discontinuing imiquimod, he experienced suspected vasculitis on his hands and feet and was hospitalized. On an unknown date, he was diagnosed with coagulopathy, skin necrosis, and blood clots to arms and legs. Dermatopathology reports show intravascular fibrin compatible with vasculopathy / coagulopathy; subsequent reports show evidence of vasculopathy no longer evident (5 days after admission), abdomen consistent with leukocytoclastic vasculitis with bland thrombi in the superficial perivascular dermis (16 days after admission). Peripheral smear reports 6 days after admission show severe thrombocytosis. Approximately one month after admission, he had an IgM positive titer and thrombocytopenia. He died ~2 months after the initial hospitalization (cause unknown). Medical history included rheumatoid arthritis, polymyalgia rheumatica, multiple skin cancers, rosacea, contact dermatitis, contact allergies, and allergies (penicillin, "bronopolon," "TCMX," and bacitracin); concomitant medications included prednisone, Centrum silver, and fish oil. He was also treated with imiquimod (dosing and duration unknown) ~1.5 years prior.
4870908	Great Britain, E (2005) Study Literature	68, F	Death	Used 3x/week for 3 weeks, warts and skin dysplasia	Study subject hospitalized 14 days after starting imiquimod because her left arm became cold/blue and no pulse could be detected. An emergency embolectomy was done successfully due to an embolus in the left brachial artery and she was treated with heparin and warfarin. Imiquimod was not discontinued. On an unspecified date, she was admitted for a left brachial embolectomy due to a further embolus . Her left arm was amputated on an unspecified date. The patient died 46 days after starting imiquimod. Medical history included renal transplant 25 years prior (and subsequent arteriopathy), non-functioning A-V fistula in right arm, squamous cell carcinoma, and high cholesterol; concomitant medications include prednisolone, azathioprine, atorvastatin, and cyclosporine.
4379844	Belgium, E (2004)	78, F	Death	Used 3x/week, metastases of melanoma on leg	Patient experienced a pulmonary thrombus and died within 3 months of starting imiquimod. Medical history included an excision of a large melanoma on her left foot 4 years prior to starting imiquimod; concomitant medications were not reported.

4544986	US, E (2005)	80, M	Hospitalization	1 sachet used 3x/week for 33 days, AK on forehead	Patient experienced flu-like symptoms, fever, enlarged lymph nodes, and elevated liver and muscle enzymes (values unspecified) ~2 weeks after starting imiquimod. Imiquimod was discontinued and he began to recover. The patient was hospitalized on an unknown date. Ten days later, imiquimod was restarted and all the events recurred (including an <u>elevated creatinine phosphokinase</u> of 900; units and normal range not reported). Repeat labs done 2 days later showed no changes in the values. Imiquimod was discontinued and the patient recovered. The reporter stated that the patient was on many concomitant medications and had a medical history; however, details were not provided.
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Abbreviations: NS=Not stated, E=Expedited (15-day), D=Direct, sBCC=Superficial basal cell carcinoma, BCC=Basal cell carcinoma, AK=Actinic keratosis, TIA=Transient ischemic attack, MI=Myocardial infarction, SVT=Supraventricular tachycardia

8.5 APPENDIX E. DATA MINING RESULTS FOR PREFERRED TERMS RELATED TO THIS REVIEW, SORTED BY DESCENDING EB05 VALUE

Preferred Terms Related to Pancytopenia

Preferred Terms	N	EB05	EBGM	EB95
Bone marrow myelogram abnormal	1	0.32	1.37	4.32

Preferred Terms Related to Lymphoma

Preferred Terms	N	EB05	EBGM	EB95
Lymphoma	4	0.64	1.47	2.98
Non-Hodgkin's lymphoma	2	0.47	1.43	3.58
Mantle cell lymphoma	1	0.31	1.35	4.23
Mycosis fungoides	1	0.28	1.21	3.77

Preferred Terms Related to Ischemic heart disease, Thromboembolic events, and Arrhythmias

Preferred Terms	N	EB05	EBGM	EB95
Paresis	2	0.43	1.32	3.31
Peripheral embolism	1	0.27	1.16	3.59
Lacunar infarction	1	0.26	1.11	3.43
Pulmonary thrombosis	1	0.26	1.09	3.39
Thrombosis	3	0.25	0.64	1.41
Acute coronary syndrome	1	0.24	1.01	3.12
Monoparesis	1	0.21	0.90	2.77
Venous thrombosis	1	0.20	0.83	2.58
Sudden death	2	0.18	0.54	1.34
Arteriosclerosis coronary artery	1	0.17	0.72	2.23
Blindness transient	1	0.17	0.71	2.21
Arterial occlusive disease	1	0.16	0.70	2.16
Disseminated intravascular coagulation	2	0.15	0.45	1.12
Cerebrovascular accident	4	0.13	0.29	0.58
Heart rate irregular	1	0.12	0.51	1.57
Supraventricular tachycardia	1	0.12	0.50	1.55
Palpitations	5	0.12	0.26	0.49
Embolism	1	0.10	0.41	1.28
Syncope	4	0.10	0.24	0.48
Cerebral infarction	1	0.09	0.39	1.20
Electrocardiogram abnormal	1	0.08	0.35	1.09
Tachycardia	4	0.08	0.18	0.36
Transient ischaemic attack	1	0.08	0.35	1.07
Haemorrhagic stroke	1	0.07	0.32	0.98
Angina pectoris	1	0.07	0.28	0.87
Heart rate increased	2	0.06	0.18	0.46
Myocardial infarction	3	0.06	0.15	0.34
Arrhythmia	1	0.04	0.16	0.50
Atrial fibrillation	1	0.04	0.19	0.59
Blood creatine phosphokinase increased	1	0.03	0.13	0.39
Loss of consciousness	1	0.02	0.09	0.27

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/s/

NAMITA KOTHARY
08/12/2009

IDA-LINA DIAK
08/12/2009

MARK I AVIGAN
08/12/2009

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: August 3, 2009

TO: Kelisha Turner, Regulatory Project Manager
Milena Lolic, M.D., Medical Officer
Division of Dermatology and Dental Drug Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22-483

APPLICANT: Graceway Pharmaceuticals, LLC.

DRUG: Tradename (Imiquimod) Cream, 3.75%

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of actinic keratoses (AKs) in immunocompetent adult patients

CONSULTATION REQUEST DATE: March 16, 2009

DIVISION ACTION GOAL DATE: October 19, 2009

PDUFA DATE: October 19, 2009

I. BACKGROUND:

The conduct of Protocol #GW01-0704 entitled “A Phase 3, Randomized, Double-blinded, Placebo-controlled, Multicenter, Efficacy and Safety Study of Four Weeks of Treatment with Imiquimod Creams for Actinic Keratoses” was inspected.

The primary objective of this study was to assess the safety and efficacy of 2.5% Imiquimod cream and 3.75% Imiquimod cream as compared to placebo in the treatment of AKs when applied once daily for two 2-week treatment cycles by a period of two weeks of non-treatment.

The review division selected the sites of Drs. Draelos and Jarratt because Dr. Draelos’ site did not use the IVRS system to randomize five subjects. These subjects were randomized by the clinical site itself. This site also reported substantial efficacy and no adverse events. Dr. Jarratt’s site had substantial efficacy and a relatively large number of subjects.

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ # of Subjects/	Inspection Dates	Final Classification
Site 30 Zoe Draelos, MD 2444 North Main Street High Point, NC 27262 336-841-2040 (P) 336-841-2044 (F)	GW01-0704/ 15/	20-22 May 2009	NAI
Site 34 Michael Jarratt, MD DermResearch, Inc 8140 N. Mopac, Bldg. 3, Suite 120 Austin, TX 78759 512-349-9889 (P)	GW01-0704/ 26/	1-8 Jun 2009	VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;

EIR has not been received from the field and complete review of EIR is pending.

1. Zoe Draelos, MD
2444 North Main Street
High Point, NC 27262

- a. **What was inspected:** The records of the 15 enrolled subjects were audited. Records reviewed included, but were not limited to, primary efficacy data, adverse events, concomitant medications, informed consent forms (ICFs), inclusion/exclusion criteria, and test article accountability.
- b. **General observations/commentary:** Review of the records noted above revealed no significant discrepancies/regulatory violations. As a result of erroneous communications with the firm responsible for randomization, five subjects (#s 405, 407, 409, 414, and 417) were manually randomized to treatment by the clinical site. The subjects appear to have been randomized appropriately and dispensed appropriate randomized therapy.
- c. **Assessment of data integrity:** Data appear acceptable in support of the respective application

2. Michael Jarratt, MD
DermResearch, Inc
8140 N. Mopac, Bldg. 3, Suite 120
Austin, TX 78759

- a. **What was inspected:** 36 subjects were screened, 26 subjects were enrolled, and 24 completed the study. All consent forms were reviewed. Other records reviewed included, but were not limited to, counts of actinic keratosis (AK) lesions, IRB and monitor correspondence, concomitant medications, adverse events, laboratory results, and study drug compliance.
- b. **General observations/commentary:** Inspection revealed that study enrollment documents for Subjects 413, 416, 420, and 430, were signed and dated after these subjects were enrolled. According to the clinical investigator's written response, these documents were completed prior to subject enrollment but were inadvertently not signed and dated until later. As such, this is a documentation issue, and review of the source records indicate that subjects were enrolled appropriately. Study drug reconciliation was inadequate in that there was an incomplete accounting for all drug packets dispensed to Subjects 408, 421 and 435. There appears to be no issue with regards to appropriate drug dispensation or subjects receiving the appropriate randomized therapy.
- c. **Assessment of data integrity:** Data appear acceptable in support of the respective application.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical investigator sites were inspected in support of this application. The data generated by the clinical sites of Drs. Draelos and Jarratt appear acceptable in support of the respective application.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

ROY A BLAY
08/06/2009

TEJASHRI S PUROHIT-SHETH
08/06/2009



**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: May 08, 2009

To: Cathy A. Miller, BSN, MPH
Safety Evaluator
Division of Medication Error and Prevention Analysis
Office of Surveillance and Epidemiology

Through: Laura Governale, PharmD, MBA
Drug Use Data Analyst Team Leader
Division of Epidemiology
Office of Surveillance and Epidemiology

From: Patty Greene, PharmD
Drug Use Data Analyst
Division of Epidemiology
Office of Surveillance and Epidemiology

Subject: Total dispensed prescriptions by physician specialty, indications for use, and concurrent conditions associated with use for Aldara[®] (imiquimod) cream

Drug Name(s): Aldara[®] (imiquimod) cream

Application Type/Number: NDA 20-723

Applicant/sponsor: Graceway Pharmaceuticals

OSE RCM #: 2009-487

1 INTRODUCTION

The Division of Medication Error and Prevention Analysis (DMEPA) is evaluating the proposed trade name, Zyclara cream (imiquimod), NDA 22-483, which has a pending application for a new 3.75% strength, dosing schedule (once daily), and treatment duration (two 2-week cycles with an interim 2-week no treatment period) for the treatment of actinic keratosis. In support of that review, the Division of Epidemiology (DEPI) has been requested to provide total dispensed prescriptions by physician specialty, indications for use, and concurrent conditions associated with use for Aldara[®] (imiquimod) 5% cream for years 2004 through 2008. Aldara[®] (imiquimod) 5% cream is approved for nonhyperkeratotic, nonhypertrophic actinic keratoses on the face or scalp in immunocompetent adults, biopsy-confirmed, primary superficial basal cell carcinoma in immunocompetent adults, and external genital and perianal warts/condyloma acuminata in patients 12 years or older.

2 METHODS AND MATERIAL

2.1 DETERMINING SETTINGS OF CARE AND DATA SOURCES USED

IMS Health, IMS National Sales Perspectives[™] data (*see Appendix I*) were used to determine the setting in which Aldara[®] (imiquimod) cream was sold. Sales of this product by number of packs (boxes) sold from the manufacturer into the various retail and non-retail channels of distribution were analyzed for year 2008 (*data not provided*).¹ During the review period, retail settings (chain stores, independent pharmacies, and food stores) accounted for the majority of Aldara[®] (imiquimod) cream sales (86%) and approximately 9% were sold to non-retail settings. Thus, the examination of Aldara[®] (imiquimod) cream utilization patterns focused on the outpatient setting, excluding mail order channels.

2.2 DATA SOURCES

Proprietary drug use databases licensed by the Agency were used to conduct this analysis. We examined total dispensed prescriptions by prescribing specialties for Aldara[®] (imiquimod) cream using SDI, Vector One[®]: National (VONA) (see Appendix 1 for full description) for calendar years 2004 through 2008. Indications associated with the use of Aldara[®] (imiquimod) cream as reported by office-based physicians, were determined using SDI's Physician Drug and Diagnosis Audit (PDDA) for calendar years 2004 through 2008.

3 DATA

3.1 PRESCRIBING SPECIALTY

Table 1 in Appendix 2 shows the total number of prescriptions dispensed for Aldara[®] (imiquimod) cream by physician specialty. The majority of prescriptions dispensed for Aldara[®] (imiquimod) cream were prescribed by Dermatology with 44% followed by General Practice/Family Medicine/Doctor of Osteopathy and Ob/Gyn with 13% and 9%, respectively, in year 2008. Less than 1% of prescriptions dispensed for Aldara[®] (imiquimod) cream were prescribed by Oncology for the entire review period.

¹ IMS Health, IMS Nationals Sales Perspectives[™], Data extracted 4-27-2009, Source file: 0904imiq.DVR

3.2 INDICATIONS FOR DRUG USE

According to office-based physician practices in the U.S., “Viral Warts” (ICD-9 078.1) was the top diagnosis code associated with the use of Aldara[®] (imiquimod) cream at ~70% for calendar year 2008. The second most common use for Aldara[®] (imiquimod) cream was “Actinic Keratosis” (ICD-9 702.0) at ~10% for the same period (*Table 2*).

3.3 CONCURRENT CONDITIONS ASSOCIATED WITH USE

We also examined concurring conditions to see what other conditions were being treated with the primary condition at the same office visit. During calendar years 2004 through 2008, when Aldara[®] (imiquimod) cream was reported for the use of “Viral Warts” (ICD-9 078.1), approximately 84% of the time this condition was the only associated diagnosis code.

For the same time period, when Aldara[®] (imiquimod) cream was reported for the use of “Actinic Keratosis” (ICD-9 702.0), approximately 80% of the time office-based physicians reported this condition as the only associated diagnosis code. Approximately 5% of the time “Malig NEO Skin NOS” (ICD-9 173.9) was reported as a concurrent condition with “Actinic Keratosis” (ICD-9 702.0). Conversely, “Actinic Keratosis” (ICD-9 702.0) was reported as a concurrent condition approximately 6% of the time when “Malig NEO Skin NOS” (ICD-9 173.9) was the primary condition (*Table 3*).

4 DISCUSSION

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that Aldara[®] (imiquimod) cream is distributed primarily to the outpatient setting based on the IMS Health, IMS National Sales Perspectives[™]. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these outpatient retail pharmacy channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

Indications for use were obtained using SDI’s PDDA, a monthly survey of 3,200 office based physicians. Although PDDA data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, PDDA data are best used to identify the typical uses for the products in clinical practice, and the VONA outpatient prescription data to evaluate trends over time.

5 CONCLUSIONS

The majority of prescriptions dispensed for Aldara[®] (imiquimod) cream were prescribed by Dermatology with 44% followed by General Practice/Family Medicine/Doctor of Osteopathy and Ob/Gyn with 13% and 9%, respectively, in year 2008. “Viral Warts” (ICD-9 078.1) was the top diagnosis code associated with the use of Aldara[®] (imiquimod) cream at ~70% for calendar year 2008. When Aldara[®] (imiquimod) cream was reported for the use of “Actinic Keratosis” (ICD-9 702.0), a concurrent condition of “Malig NEO Skin NOS” (ICD-9 173.9) existed approximately 5% of the time.

APPENDIX 1: Database Descriptions

SDI, LLC: Vector One®: National (VONA)

SDI's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over (b) (4) claims per year, representing over (b) (4) unique patients. Since 2002 Vector One has captured information on over (b) (4) representing (b) (4) unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

SDI, LLC: Physician Drug & Diagnosis Audit (PDDA)

SDI's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from approximately 3,100 office-based physicians representing 29 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

SDI uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

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/s/

PATTY A GREENE
09/08/2009

LAURA A GOVERNALE
09/10/2009

DSI CONSULT: Request for Clinical Inspections

Date: March 16, 2009

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1, HFD-46
Joe Salewski., Branch Chief (Acting), GCP2, HFD-47

Through: Milena Lolic, M.D., Medical Officer, Division of Dermatology and Dental Products/HFD-540
Jill Lindstrom, M.D., Clinical Team Leader, Division of Dermatology and Dental Products/HFD-540

From: Kelisha Turner, Regulatory Health Project Manager, HFD-540
Division of Dermatology and Dental Products

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 22-483
Sponsor: Graceway Pharmaceuticals, LLC.
Drug: Tradename (imiquimod) Cream, 3.75%
NME: No
Standard or Priority: Standard
Study Population > 18 years of age: adult patients
Pediatric exclusivity: Waiver Requested

PDUFA: October 19, 2009
Action Goal Date: October 19, 2009
Inspection Summary Goal Date: August 5, 2009

II. Background Information

Graceway Pharmaceuticals, submitted a New Drug Application for imiquimod 3.75% cream for the treatment of actinic keratoses in immunocompetent adult patients.

Study 704 is a randomized, double-blind vehicle-controlled study to assess the efficacy and safety of imiquimod 2.5% and 3.75% cream. The study enrolled 237 subjects at 13 centers (79 with 2.5% imiquimod, 79 with 3.75% imiquimod, and 79 vehicle). Subjects were followed for 14 weeks and the treatment regimen involved two 2-week treatment cycles separated by a 2-week no-treatment period. The sponsor also conducted an identical study (702) that enrolled 242 subjects at 13 centers (81 with 2.5% imiquimod, 81 with 3.75% imiquimod, and 80 vehicle).

III. Protocol/Site Identification

Site # (Name, Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
Site 30 Zoe Draelos, MD 2444 North Main Street High Point, NC 27262 336-841-2040 (P) 336-841-2044 (F)	704	15	Actinic Keratoses
Site 34 Michael Jarratt, MD DermResearch, Inc 8140 N. Mopac, Bldg. 3, Suite 120 Austin, TX 78759 512-349-9889 (P)	704	26	Actinic Keratoses

IV. Site Selection/Rationale

Selection of the sites listed above is as follows:

- Site 30- Dr. Zoe Draelos’ site did not use the IVRS (ClinPhone) to randomize 5 subjects and ‘self-randomized’ these subjects instead. The site also had large efficacy and no reported adverse reactions. We are particularly interested in any information regarding the randomization problems.
- Site 34- Dr. Michael Jarratt’s site had large efficacy and a relatively large number of subjects.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): IVRS problems, see above.

International Inspections: Not Applicable to this application

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

V. Tables of Specific Data to be Verified (if applicable)

Should you require any additional information, please contact Kelisha Turner, Regulatory Project Manager, at 301-796-0766 or Milena Lolic, Medical Officer, at 301-796-3825.

Concurrence:

Milena Lolic, M.D., Clinical Reviewer
Jill Lindstrom, M.D., Clinical Team Leader

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/s/

Jill Lindstrom
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Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: May 28, 2009

From: CDER DCRP QT Interdisciplinary Review Team and the Division of Cardiovascular and Renal Products

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Kelisha Turner
Regulatory Project Manager
Division of Dermatology and Dental Products

Subject: QT-IRT Consult to NDA 22483

This memo responds to your consult to us dated 21 April 2009 regarding QT waiver request for Imiquimod 3.75% cream for the treatment of Actinic Keratosis (AK) under NDA 22483 sponsored by Graceway Pharmaceuticals LLC. The QT-IRT received and reviewed the following materials:

- Your consult
- ODS review (2005) of cardiac events with Imiquimod.
- Summary of Clinical Safety (eCTD 2.7.4)

Questions from the Review Division:

1. Has the applicant adequately addressed the potential of their product to impact cardiac repolarization?

QT-IRT Response:

No, ECGs were not performed in the clinical development program for the Imiquimod 3.75% crème, including Studies 1520-IMIQ and 1402-IMIQ where subjects had supra-therapeutic exposures. Cardiac AEs in the studies were confounded because of co-morbidities and concomitant medications but no ECG effects are reported in the narratives.

2. Are additional data needed to address the potential for QT/QTc interval prolongation?

QT-IRT Response:

The incidence of AEs related to QT prolongation with Aldara was similar to the background rate in the general population in our MGPS data mining analysis (see analysis for AEs related to QT prolongation under reviewer's assessments). However, if the Division is concerned about the potential of affect cardiac repolarization, then the sponsor should conduct a TQT study. Also see response to Question 1.

3. Are there any additional studies needed to address the effect of imiquimod on cardiac system?

QT-IRT Response:

We conducted an MGPS data mining analysis of the AERS database for preferred terms (PTs) related to thromboembolism and myocardial ischemia with Imiquimod. The signal scores suggested that the incidence was similar/less than the background rate in the general population (see reviewer's assessments). However, we recommend that the division also consults the Office of Surveillance and Epidemiology in this regard.

Background

Imiquimod is a topical immune response modifier currently approved as 5% cream (Aldara) for 3 indications (genital warts in 1997, basal cell CA and limited area AK in 2004). The Aldara treatment regimen for AK is 2 times a week for 16 weeks.

In NDA 22-483, the applicant seeks approval of imiquimod 3.75% cream for the treatment of actinic keratosis. The new formulation and regimen, that is 3.75% imiquimod cream in a 2-week treatment cycle regimen, treats a larger area (full face or scalp >25 cm² vs. ≤25 cm² for Aldara) for a shorter duration (two 2-week cycles with an interim 2-week no-treatment period vs. the 16-week regimen for Aldara), and with a more intuitive dosing regimen (daily dosing vs. twice weekly dosing for Aldara). No QT study was performed for either concentration or dosing regimen; the applicant's justification is that 3.75% cream has less systemic exposure than the 5% and that current marketing experience with 5% demonstrates the safe cardiac profile of the drug.

However, the division has the following concerns:

1) ODS review of 1366 AERS cases from 2005 states that imiquimod could have contributed to 12 cardiac events and 6 deaths,

(b) (4)

3) No ECG studies were done in imiquimod development program.

Non-Clinical Overview

Safety Pharmacology Studies per the ICH S7B guidelines were not performed

Previous Clinical Experience

“Aldara received its first approval from the U.S. Food and Drug Administration (FDA) on February 27, 1997 for the treatment of adults with EGW (extra-genital warts) Imiquimod is a Toll-like receptor 7 agonist that activates the innate and adaptive immune responses. This activation can lead to inflammation in the skin. Consistent with its pharmacological effects, application site reactions, which were identified by the clinical research program leading to registration, have been the most common adverse event observed since imiquimod 5% cream was approved.”

ODS Review

“We were asked to provide an overview of AERS data and an assessment of cardiac events for imiquimod, a topical immune response modifier. Imiquimod is approved for the treatment of actinic keratosis, external genital warts, and superficial basal cell carcinoma.

AERS contains a total of 1366 cases (raw count) for imiquimod. Most of the cases had non-serious outcomes, but the patients died in 12 cases and were hospitalized in 80 cases. The most frequently cited indication for use was *viral warts*. The most frequently reported events were application site reactions, which are labeled.

“Twelve cases reported cardiac events, including 4 cases of possible ischemia (chest pain-2, angina-1, myocardial infarction-1), 7 cases of arrhythmia (tachycardia-2, syncope-2, palpitation-1, sudden death-1, a fib-1), and 1 case of cardiomyopathy. This disparate set of cases included two cases of tachycardia with a positive rechallenge. The use of imiquimod could have contributed to these events.

“Additionally, we reviewed 12 cases with an outcome of death. Thromboembolic events may have led to death in 3 cases. Three additional cases may have involved suicidal intent. Although the AERS data were not compelling, a possible association between the use of imiquimod and the fatal outcome in these 6 cases could not be excluded.—

“We do not have any labeling recommendations at this time.”

Reviewer’s Comments:

Narratives were reviewed and concur with the ODS reviewer’s conclusions for the cardiac events

Except for the 71 yr old previously healthy man who had a sudden death (found dead at home), the remaining 5 cases quoted in the ODS review with possible association to imiquimod were confounded due to co-morbidities and advanced age (CLL, malignant lymphoma, acute myeloid leukemia, 98 yr old male hospitalized with male with hemolytic anemia, fatigue and hepatomegaly and an 83-year-old man with a history of Parkinson’s Disease).

Clinical Pharmacology

Systemic absorption of imiquimod across the affected skin of 17 subjects with AK was observed when 3.75% imiquimod was applied to the face and/or scalp 7 times per week for 3 weeks (18.75 mg imiquimod, 2 packets once daily). The single-dose and steady-state pharmacokinetics of imiquimod are summarized in the sponsor’s Table 2.7.2-2. Serum concentrations of the two metabolites (S-26704 and S-27700) were measured; however, few samples had concentrations above the LLOQ.

Table 2.7.2-2: Single-dose and Steady-state Pharmacokinetics of 3.75% Imiquimod Cream (Study GW01-0706)

Parameter	Mean (SD)			
	N ^c	Day 1	N ^d	Day 21
C _{max} (ng/mL)	17	0.136 (0.059)	17	0.323 (0.159)
C _{min} (ng/mL) ^a	–	NA	17	0.199 (0.109)
T _{max} (hr) ^b	17	9.0 (4.0-24.03)	17	9.0 (4.0-16.0)
AUC ₀₋₂₄ (ng•hr/mL)	17	1.831 (0.889)	17	5.974 (3.088)
AUC ₀₋₁ (ng•hr/mL)	17	1.679 (1.056)	–	NA
AUC _{0-inf} (ng•hr/mL)	11	4.443 (1.309)	–	NA
λ _z (1/hr)	11	0.0450 (0.0219)	15	0.0294 (0.0142)
T _{1/2} (hr)	10	19.818 (10.125)	15	29.260 (16.979)
R _{AUC}	–	NA	15	3.873 (2.153)
R _{Cmax}	–	NA	15	2.810 (1.514)
λ _{z,eff} (hr ⁻¹)	–	NA	15	0.0235 (0.0229)
T _{1/2,eff} (hr)	–	NA	15	55.339 (36.380)

NA=Not applicable
^a Pre-dose concentration (t=0)
^b Median (minimum-maximum)
^c Subjects 001-601 and 001-618 were BLQ, therefore unable to calculate PK parameters
^d Subject 001-619 did not have concentration data on Day 21; Subject 001-608 excluded due to missed dose on Day 20

Source: Summary of Clinical Pharmacology Studies, page 6 of 13

Steady-state systemic exposure to imiquimod is lower when 3.75% imiquimod was applied to the face and/or scalp 7 times per week for 3 weeks compared to 5% imiquimod cream (ALDARA) evaluated in Safety Study 1520-IMIQ as shown in Table 2.7.2-4.

Table 2.7.2-4 Summary of Systemic Exposure at Steady-State Following Administration of 3.75% or 5% Imiquimod Cream [Mean(SD) Serum Imiquimod Cmax and AUC_{ss}]

	Cmax (ng/mL)		AUC (ng•hr/mL)	
	Mean (SD)	Ratio ^a	Mean (SD)	Ratio ^a
Study GW01-0706 2 pkts (18.75 mg) daily to face/scalp	0.323 (0.159)		5.974 (3.088)	
Study 1520-IMIQ^b 6 pkts (75 mg) 2 x weekly to > 25% BSA	0.958 (1.18)	2.96	24.3 (26.9)	4.07
Study 1402-IMIQ 1 pkts (12.5 mg) 3x/week to face	0.120 (0.0629)	0.37	2.06 (1.70)	0.34
2 pkts (25 mg) 3x/week to scalp	0.214 (0.0968)	0.66	4.89 (4.41)	0.82
6 pkts (75 mg) 3x/week to hand/forearms ^c	1.35 (0.841)	4.18	29.1 (17.1)	4.87
6 pkts (75 mg) 3x/week to hand/forearms ^d	3.53 (6.52)	10.92	55.4 (76.0)	9.27

Pkts = packets; BSA= Body surface area
^a 5% imiquimod regimen/3.75% imiquimod regimen
^b Month 4 data
^c Data from Harrison *et al*, 2004¹ (rejecting outliers that were >5X the SD of their respective means)
^d Data from the 1402-IMIQ² report that includes outliers

According to the ALDARA label,

“Systemic absorption of imiquimod across the affected skin of 58 subjects with AK was observed with a dosing frequency of 3 applications per week for 16 weeks. Mean peak serum drug concentrations at the end of week 16 were approximately 0.1, 0.2, and 3.5 ng/mL for the applications to face (12.5 mg imiquimod, 1 single-use packet), scalp (25 mg, 2 packets) and hands/arms (75 mg, 6 packets), respectively.”

Reviewer’s Comments: ALDARA is currently approved for Actinic Keratosis and External Genital Warts at a dosing regimen of 1 packet (12.5 mg) 2 to 3 times per week for a full 16 weeks. The proposed dosing regimen for 3.75% cream will provide greater exposure compared to the approved dosing regimen of ALDARA 5% Cream for Actinic Keratosis.

Reviewer’s Assessments:

Analysis of Adverse events related to QT Prolongation

An MGPS Data mining Analysis of the AERS database for adverse events related to QT prolongation was conducted. The signal scores (EBGM values) were all less than 1, indicating incidence similar to background rate in the general population.

Configuration: CBAERS BestRep (S) **Run :** Generic (S) **Run ID:** 694
Dimension: 2 **Selection Criteria:** Generic name(Imiquimod) + PT(...)
2 rows Sorted by Generic name, EBGm desc

Generic name	Level 1	PT	HLT	N	EBGM	EB05	EB95	PRR
Imiquimod	Antivirals [D06bb]	Sudden death	Death and sudden death	2	0.539	0.176	1.34	0.909
Imiquimod	Antivirals [D06bb]	Convulsion	Seizures and seizure disorders NEC	3	0.098	0.038	0.215	0.117

ID:	694
Type:	MGPS
Name:	Generic (S)
Description:	Generic; Suspect drugs only; Minimum count=1; Standard strata (Age, FDA Year, Gender); includes PRR and ROR; includes hierarchy information
Project:	CBAERS Standard Runs
Configuration:	CBAERS BestRep (S)
Configuration Description:	CBAERS data; best representative cases; suspect drugs only; with duplicate removal
As Of Date:	05/07/2009 00:00:00
Item Variables:	Generic name, PT
Stratification Variables:	Standard strata
Highest Dimension:	2
Minimum Count:	1
Calculate PRR:	Yes
Calculate ROR:	Yes
Base Counts on Cases:	Yes
Use "All Drugs" Comparator:	No
Apply Yates Correction:	Yes
Stratify PRR and ROR:	No
Fill in Hierarchy Values:	Yes
Exclude Single Itemtypes:	Yes
Fit Separate Distributions:	Yes
Save Intermediate Files:	No
Created By:	Empirica Signal Administrator
Created On:	05/15/2009 06:04:05 EDT
User:	Suchitra Balakrishnan
Source Database:	Source Data: CBAERS data from Extract provided by CBER as of 05/07/2009 00:00:00 loaded on 2009-05-14 06:42:10.0

Dimension: 2 **Selection Criteria:** Generic name(Imiquimod) + PT(Cardiac arrest, Convulsion, Electrocardiogram QT prolonged, Sudden cardiac death, Sudden death, Torsade de pointes, Ventricular arrhythmia, Ventricular fibrillation, Ventricular flutter, Ventricular tachyarrhythmia, Ventricular tachycardia)

```
SELECT * FROM OutputData_694 WHERE (DIM=2 AND ((P1='D' AND ITEM1 IN ('Imiquimod') AND P2='E' AND ITEM2 IN ('Cardiac arrest','Convulsion','Electrocardiogram QT prolonged','Sudden cardiac death','Sudden death','Torsade de pointes','Ventricular arrhythmia','Ventricular fibrillation','Ventricular flutter','Ventricular tachyarrhythmia','Ventricular tachycardia')))) ORDER BY ITEM1,EBGM desc
```

These data do not, by themselves, demonstrate causal associations; they may serve as a signal for further investigation.

Analysis for thromboembolic events and AEs related to myocardial ischemia

We also conducted an MGPS data mining analysis for PTs related to myocardial ischemia and thromboembolism-(see below). The EBGm values for the PTs analyzed were all ≤ 1 ; indicating incidence was similar/less to the background rate in the general population.

Configuration: CBAERS BestRep (S) **Run :** Generic (S) **Run ID:** 694
Dimension: 2 **Selection Criteria:** Generic name(Imiquimod) + PT(...)
15 rows Sorted by Generic name, EBGm desc

Generic name	Level 1	PT	HLT	N	EBGM	EB05	EB95	PRR
Imiquimod	Antivirals [D06bb]	Acute coronary syndrome	Ischaemic coronary artery disorders	1	1.02	0.238	3.15	2.03
Imiquimod	Antivirals [D06bb]	Venous thrombosis	Non-site specific embolism and thrombosis	1	0.836	0.196	2.59	2.43
Imiquimod	Antivirals [D06bb]	Thrombosis	Non-site specific embolism and thrombosis	3	0.644	0.251	1.42	0.568
Imiquimod	Antivirals [D06bb]	Cerebral haemorrhage	Central nervous system haemorrhages and cerebrovascular accidents	1	0.613	0.144	1.90	0.544
Imiquimod	Antivirals [D06bb]	Cardiac failure	Heart failures NEC	4	0.541	0.237	1.10	0.536
Imiquimod	Antivirals [D06bb]	Embolism	Non-site specific embolism and thrombosis	1	0.414	0.097	1.28	0.700
Imiquimod	Antivirals [D06bb]	Cerebral infarction	Central nervous system haemorrhages and cerebrovascular accidents	1	0.390	0.091	1.21	0.390
Imiquimod	Antivirals [D06bb]	Cardiomyopathy	Cardiomyopathies	1	0.357	0.084	1.11	0.495
Imiquimod	Antivirals [D06bb]	Haemorrhagic stroke	Central nervous system haemorrhages and cerebrovascular accidents	1	0.318	0.075	0.986	0.378
Imiquimod	Antivirals [D06bb]	Cerebrovascular accident	Central nervous system haemorrhages and cerebrovascular accidents	4	0.288	0.126	0.583	0.226
Imiquimod	Antivirals [D06bb]	Angina pectoris	Ischaemic coronary artery disorders	1	0.284	0.066	0.878	0.212
Imiquimod	Antivirals [D06bb]	Chest pain	Pain and discomfort NEC	9	0.228	0.130	0.377	0.309
Imiquimod	Antivirals [D06bb]	Cardiac failure congestive	Heart failures NEC	1	0.176	0.041	0.546	0.115
Imiquimod	Antivirals [D06bb]	Chest discomfort	Pain and discomfort NEC	1	0.161	0.037	0.498	0.190
Imiquimod	Antivirals [D06bb]	Myocardial infarction	Ischaemic coronary artery disorders	2	0.111	0.036	0.277	0.085

ID:	694
Type:	MGPS
Name:	Generic (S)
Description:	Generic; Suspect drugs only; Minimum count=1; Standard strata (Age, FDA Year, Gender); includes PRR and ROR; includes hierarchy information
Project:	CBAERS Standard Runs
Configuration:	CBAERS BestRep (S)
Configuration Description:	CBAERS data; best representative cases; suspect drugs only; with duplicate removal
As Of Date:	05/07/2009 00:00:00

Item Variables:	Generic name, PT
Stratification Variables:	Standard strata
Highest Dimension:	2
Minimum Count:	1
Calculate PRR:	Yes
Calculate ROR:	Yes
Base Counts on Cases:	Yes
Use "All Drugs" Comparator:	No
Apply Yates Correction:	Yes
Stratify PRR and ROR:	No
Fill in Hierarchy Values:	Yes
Exclude Single Itemtypes:	Yes
Fit Separate Distributions:	Yes
Save Intermediate Files:	No
Created By:	Empirica Signal Administrator
Created On:	05/15/2009 06:04:05 EDT
User:	Suchitra Balakrishnan
Source Database:	Source Data: CBAERS data from Extract provided by CBER as of 05/07/2009 00:00:00 loaded on 2009-05-14 06:42:10.0

Dimension: 2 Selection Criteria: Generic name(Imiquimod) + PT(Acute coronary syndrome, Acute left ventricular failure, Acute myocardial infarction, Acute right ventricular failure, Angina pectoris, Angina unstable, Arterial thrombosis, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiomyopathy, Cardiomyopathy acute, Cerebral haemorrhage, Cerebral infarction, Cerebral ischaemia, Cerebrovascular accident, Cerebrovascular disorder, Chest discomfort, Chest pain, Coronary artery disease, Coronary artery embolism, Coronary artery thrombosis, Embolic stroke, Embolism, Embolism venous, Haemorrhage intracranial, Haemorrhagic stroke, Ischaemic cardiomyopathy, Ischaemic stroke, Left ventricular failure, Low cardiac output syndrome, Myocardial depression, Myocardial fibrosis, Myocardial infarction, Myocardial ischaemia, Myocarditis, Right ventricular failure, Thrombosis, Thrombotic stroke, Vasculitis cerebral, Venous thrombosis, Ventricular dysfunction, Ventricular dyskinesia, Ventricular hypokinesia)

```
SELECT * FROM OutputData_694 WHERE (DIM=2 AND ((P1='D' AND ITEM1 IN ('Imiquimod') AND P2='E' AND ITEM2 IN ('Acute coronary syndrome','Acute left ventricular failure','Acute myocardial infarction','Acute right ventricular failure','Angina pectoris','Angina unstable','Arterial thrombosis','Cardiac failure','Cardiac failure acute','Cardiac failure congestive','Cardiomyopathy','Cardiomyopathy acute','Cerebral haemorrhage','Cerebral infarction','Cerebral ischaemia','Cerebrovascular accident','Cerebrovascular disorder','Chest discomfort','Chest pain','Coronary artery disease','Coronary artery embolism','Coronary artery thrombosis','Embolic stroke','Embolism','Embolism venous','Haemorrhage intracranial','Haemorrhagic stroke','Ischaemic cardiomyopathy','Ischaemic stroke','Left ventricular failure','Low cardiac output syndrome','Myocardial depression','Myocardial fibrosis','Myocardial infarction','Myocardial ischaemia','Myocarditis','Right ventricular failure','Thrombosis','Thrombotic stroke','Vasculitis cerebral','Venous thrombosis','Ventricular dysfunction','Ventricular dyskinesia','Ventricular hypokinesia')))) ORDER BY ITEM1,EBGM desc
```

These data do not, by themselves, demonstrate causal associations; they may serve as a signal for further investigation.

Thank you for requesting our input into the development of this product under IND. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

APPENDIX:

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

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

/s/

Suchitra Balakrishnan
5/28/2009 12:42:50 PM
MEDICAL OFFICER

Christine Garnett
5/28/2009 02:43:49 PM
BIOPHARMACEUTICS

Norman Stockbridge
5/28/2009 03:54:14 PM
MEDICAL OFFICER

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Dermatology and Dental Products

Application Number: NDA 22-483

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

Applicant: Graceway Pharmaceuticals, LLC.

Material Reviewed:

Submission Date(s): December 19, 2008

Receipt Date(s): December 19, 2008

Submission Date of Structure Product Labeling (SPL): December 19, 2008

Type of Labeling Reviewed: SPL

Background and Summary

NDA 22-483, Tradename (imiquimod) Cream, 3.75%, submitted December 19, 2008 is indicated for the topical treatment of clinically typical visible or palpable actinic keratoses of the face or balding scalp in immunocompetent adults. Aldara (imiquimod) Cream 5% is currently approved under NDA 20-723 for the treatment of actinic keratosis, with a 16-week regimen of twice weekly dosing for a defined 25cm² treatment area.

Review

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

In the Highlights section:

1. Initial U.S. Approval includes the year (b) (4). The “initial U.S. Approval” should be followed by the four-digit year in which FDA initially approved a new molecular entity, new biological product, or new combination of active ingredients.
2. For a new NDA, the revision date should be left blank at the time of submission and be edited to the month/year of application approval. The revised date currently reads (b) (4).

In the Contents (Table of Contents) section:

3. Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading. See the Patient Counseling Information section and the Patient Package Insert (PPI), General information about TRADENAME Cream.
4. The headings and subheadings should be named and numbered correctly as outlined under 21 CFR 201.56 (d)(1). Please address the following:
 - In sections 6.2 and 6.3 omit (b) (4) and (b) (4) (b) (4) (modifications should also be made to the Full Prescribing Information (FPI) section).
 - The word (b) (4) in sections 8 and 13 should be omitted (modifications should also be made to the FPI section).
 - Storage and Handling is not included in the header of section 16 (modifications should also be made to the FPI section).
5. The first letters of “Full Prescribing Information” at the end of the Contents should be in capital letters (*Sections or subsections omitted from the Full Prescribing Information are not listed.).

In the Full Prescribing Information section:

6. Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format. (See PPI).
7. Do not refer to adverse reactions as “adverse events” (See language under 6.1, Table 3). Please refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format,” available at <http://www.fda.gov/cder/guidance>.

Recommendations

Please address the identified labeling deficiencies/issues and re-submit labeling by April 28, 2009. This updated version of labeling will be used for further labeling discussions.

Kelisha C. Turner
Regulatory Project Manager

Supervisory Comment/Concurrence:

Margo Owens
Team Leader, Project Management Staff

Drafted: KT/1-23-2009

Revised/Initialed: MO/2-23-2009

Finalized: KT/2-23-2009

Filename: CSO Labeling Review Template (updated 1-16-07).doc

CSO LABELING REVIEW OF PLR FORMAT

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this page is the manifestation of the electronic signature.**

/s/

Kelisha Turner
2/23/2009 05:44:37 PM
CSO

Margo Owens
2/26/2009 04:20:49 PM
CSO