

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22483Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 022483

SUPPL # n/a

HFD # 540

Trade Name Zyclara Cream, 3.75%

Generic Name imiquimod

Applicant Name Graceway Pharmaceuticals, LLC

Approval Date, If Known PDUFA Goal Date March 29, 2010

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

n/a

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

n/a

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Three

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 020723

Aldara (imiquimod) Cream, 5%

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

GW01-0702, GW01-0704

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

N/A

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

GW01-0702, GW01-0704

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 049480 YES !
! ! NO
! Explain:

Investigation #2
IND # 049480 YES !
! ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====

Name of person completing form: Kelisha C. Turner

Title: Regulatory Health Project Manager

Date: March 18, 2010

Name of Office/Division Director signing form: Susan J. Walker, M.D., F.A.A.D.

Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/

KELISHA C TURNER
03/24/2010

JILL A LINDSTROM
03/24/2010

SUSAN J WALKER
03/24/2010

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-483 Supplement Number: N/A NDA Supplement Type (e.g. SE5): _____

Division Name: DDDP PDUFA Goal Date: 10/19/09 Stamp Date: 12/19/2008

Proprietary Name: Zyclara (pending)

Established/Generic Name: imiquimod

Dosage Form: Cream, 3.75%

Applicant/Sponsor: Graceway Pharmaceuticals, LLC.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) Actinic Keratosis
- (2) External Genital Warts
- (3) Superficial Basal Cell Carcinoma
- (4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Actinic Keratosis on the face and/or scalp

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
 No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)

Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:					
Population		minimum	maximum		
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.		

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Action F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):
Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

Necessary studies would be impossible or highly impracticable because:

- Disease/condition does not exist in children
- Too few children with disease/condition to study
- Other (e.g., patients geographically dispersed): _____

Not meaningful therapeutic benefit:

Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Action C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Population	minimum	maximum	Ready for Approval in Adults
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is properly labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

ite: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

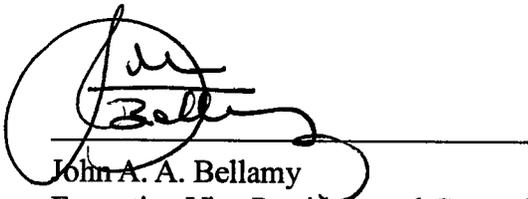
FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

1.3.3 Debarment Certification

DEBARMENT CERTIFICATION

Graceway Pharmaceuticals, LLC hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

A handwritten signature in black ink, appearing to read "John A. A. Bellamy", is written over a horizontal line. The signature is stylized and includes a large circular flourish on the left side.

John A. A. Bellamy
Executive Vice President and General Counsel
Graceway Pharmaceuticals, LLC

30 JAN '09

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 022483 BLA #	NDA Supplement # N/A BLA STN #	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: Zyclara Established/Proper Name: imiquimod Dosage Form: cream, 3.75%		Applicant: Graceway Pharmaceutical, LLC Agent for Applicant (if applicable): N/A
RPM: Kelisha Turner		Division: Division of Dermatology and Dental Products
<p>NDAs: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ User Fee Goal Date Action Goal Date (if different)		3-29-2010; 10-19-2009 3-25-2010; 10-16-2009
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (<i>specify type and date for each action taken</i>)		<input type="checkbox"/> None CR 10-16-2009
❖ Promotional Materials (<i>accelerated approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received N/A

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics ²	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 5 <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC (required for approvals only) If PeRC review not necessary, explain: _____	June 24, 2009
❖ BLAs only: RMS-BLA Product Information Sheet for TBP has been completed and forwarded to OBPS/DRM (approvals only)	<input type="checkbox"/> Yes, date N/A
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No N/A
❖ Public communications (approvals only)	N/A
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new RMS-BLA Product Information Sheet for TBP must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner’s receipt of the applicant’s notice of certification?

Yes No

(Note: The date that the patent owner received the applicant’s notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If “Yes,” skip to question (4) below. If “No,” continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant’s notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If “No,” continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If “No,” the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If “No,” continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>CONTENTS OF ACTION PACKAGE</p>	
<p>❖ Copy of this Action Package Checklist³</p>	<p>3-29-2010</p>
<p>Officer/Employee List</p>	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Action Letters</p>	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>3-25-2010 Approval; 10-16-09 Complete Response</p>
<p>Labeling</p>	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	<p>3-25-2010</p>
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>12-19-08</p>
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	<p>N/A</p>
<p>❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)</p>	<p><input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert (incorporated into PI) <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None</p>

³ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent division proposal for (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	3-22-2010 & 2-12-2010
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Review(s) (<i>indicate date(s)</i>) • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) 	6-12-09 Review 10-7-09 Conditionally Acceptable (Reconsideration); 8-5-09 Ack. of Withdrawal 6-12-09 Unacceptable
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 2-26-09 <input checked="" type="checkbox"/> DMEDP 3-24-2010; 11-4-09 <input checked="" type="checkbox"/> DRISK 3-3-2010; 10-13-09 <input checked="" type="checkbox"/> DDMAC 2-26-2010; 9-9-09 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews

Administrative / Regulatory Documents

<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	3-24-09
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant in on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) 	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> ❖ Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>) 	3-18-2010; 2-10-2010; 2-6-2010; 1-15-2010; 12-22-2010; 10-16-09; 6-26-09; 6-18-09; 6-1-09; 5-14-09; 5-5-09; 3-19-09; 3-2-09; 12-31-08
<ul style="list-style-type: none"> ❖ Internal memoranda, telecons, etc. 	3-18-2010

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Minutes of Meetings	
• PeRC (<i>indicate date of mtg; approvals only</i>)	<input type="checkbox"/> Not applicable 6-24-09 Full Waiver Granted
• Pre-Approval Safety Conference (<i>indicate date of mtg; approvals only</i>)	<input checked="" type="checkbox"/> Not applicable
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 10-29-08
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 1-20-08 (IND 30,432)
• Other (e.g., EOP2a, CMC pilot programs)	11-17-09; 11-28-07, 10-31-07, 7-27-07
❖ Advisory Committee Meeting(s)	
• Date(s) of Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	
Division Director Summary Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3-22-2010; 10-14-09
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 3-12-2010; 9-23-09
	<input type="checkbox"/> None 1
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	See CDTL reviews
• Clinical review(s) (<i>indicate date for each review</i>)	3-23-2010; 3-12-2010; 9-23-09; 2-27-09 Filing Review
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	See clinical review 10-15-09
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	See 9-23-09 clinical review pg. 14
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None DCaRP 3-1-2010; 2-23-2010 DCaRP; ODE III 1-15-2010; DCaRP 1-7-2010; DCaRP 9-17-09; DEPI 9-10-09; DPV I 8-12-09; DCaRP 5-28-09
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Risk Management	
• REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	
• REMS Memo (<i>indicate date</i>)	
• Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	<input checked="" type="checkbox"/> None

⁵ Filing reviews should be filed with the discipline reviews.

❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	<input type="checkbox"/> None requested Clinical 8-6-09 (8-5-09, 7-29-09)
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 8-6-09; 2-2-09 Filing Review
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None 3-19-2010; 8-28-09 DSI Addendum; 8-16-09 Primary Review; 4-17-09 Filing Review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input type="checkbox"/> None 8-20-09
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 2-22-2010; 8-3-09; 2-17-09 Filing Review
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Product quality review(s) (indicate date for each review)	<input type="checkbox"/> None 3-18-2010; 9-23-09; 2-2-09 Filing Review
• ONDQA Biopharmaceutics review (indicate date for each review)	
• BLAs only: Facility information review(s) (indicate dates)	<input type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology (indicate date of each review)	

❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	9-23-09 See CMC Review pgs. 51-52
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> • NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i> 	Date completed: 9-21-09 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> • BLAs: <ul style="list-style-type: none"> ○ TBP-EER ○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) <i>(date completed must be within 60 days prior to AP)</i> 	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/

KELISHA C TURNER
03/29/2010

Turner, Kelisha C

From: Sean Brennan [sean.brennan@gracewaypharma.com]
Sent: Tuesday, March 23, 2010 4:59 PM
To: Turner, Kelisha C; Owens, Margo
Subject: NDA 22-483: Zyclara (imiquimod) cream, 3.75% - Patient's Package Insert (PPI)

Dear Ms. Turner:

Reference is made to the subject NDA and to your request to remove Graceway's website from the PPI.

Graceway agrees to remove it's website from the PPI. A revised copy will be submitted to the NDA.

If you have questions or need additional information, please contact me.

Sincerely,

Sean Brennan Ph.D.
Sr. VP, Regulatory Affairs
Graceway Pharmaceuticals, LLC

Office: 423-274-5210

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/

KELISHA C TURNER

03/24/2010

Turner, Kelisha C

From: Sean Brennan [sean.brennan@gracewaypharma.com]
Sent: Wednesday, March 17, 2010 4:31 PM
To: Owens, Margo; Turner, Kelisha C
Subject: NDA 22-483 - Postmarketing Requirement Dates

Dear Ms. Owens:

Reference is made to the subject NDA and to your phone request regarding the postmarketing requirement to conduct a clinical study.

Assuming the clinical study is of the design proposed by Graceway in the correspondence dated March 12, 2010, we commit to the following dates:

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

If you have any questions or need additional information please contact me.

Sincerely,

Sean Brennan PhD
Sr. VP, Regulatory Affairs
Graceway Pharmaceuticals, LLC

Office: 423-274-5210

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

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/s/

KELISHA C TURNER
03/23/2010

REQUEST FOR CONSULTATION

TO (Division/Office):

Mail: OSE

Attn: Janet Anderson

FROM:

Kelisha Turner, Regulatory Project Manager, 301-796-0766
Milena Lolic, MD, Clinical Reviewer, 301-796-3825
Jill Lindstrom, MD, Clinical Team Leader, 301-796-0944

DATE
3-16-2010

IND NO.

NDA NO
022483

TYPE OF DOCUMENT
Labeling/Carton & Container
Label

DATE OF DOCUMENT
3-15-2010

NAME OF DRUG
Zyclara (imiquimod) Cream,
3.75%

PRIORITY CONSIDERATION
Class 1 Resubmission

CLASSIFICATION OF DRUG
5

DESIRED COMPLETION DATE
3-18-2010

NAME OF FIRM: Graceway Pharmaceuticals, LLC

REASON FOR REQUEST

I. GENERAL

- | | | |
|--------------------------------------------------------|--------------------------------------------------|--------------------------------------------------------|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input checked="" type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- | | |
|--------------------------------------------------|-------------------------------------------------|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--------------------------------------------------|-----------------------------------------------------|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|----------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: This submission is a Complete Response - Class 1 Resubmission. Please review the labeling and carton and container label for NDA 022483 Zyclara (imiquimod) Cream, 3.75%. Attached is a copy of a substantially complete label.

Please note that discussion has been ongoing and this consult response is being submitted for documentation purposes.

Target Completion Date: 3-19-2010

PDUFA Date 3-29-2010

SIGNATURE OF REQUESTER Kelisha Turner, Regulatory Project Manager, 301-796-0766 Milena Lolic, MD, Clinical Reviewer, 301-796-3825 Jill Lindstrom, MD, Clinical Team Leader, 301-796-0944	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

22 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/

KELISHA C TURNER
03/17/2010

Turner, Kelisha C

From: Turner, Kelisha C
Sent: Monday, March 01, 2010 4:06 PM
To: Sean Brennan
Cc: Owens, Margo
Subject: RE: NDA 22-483: Labeling - Calculation of Animal Multiples of Human Exposure (sections 8.1 and 13.1)

Dr. Brennan,

The Agency's response to your February 26, 2010 email is provided below:

The calculation of multiples of human exposure for the nonclinical toxicology studies contained in the drug label should be based on the maximal use clinical conditions. Therefore, for the Zyclara cream labeling, the maximum human (b) (4)

that were used in the calculation of the multiples of human exposure were considered the exposure obtained under maximal use clinical conditions (in the case of 2 packets/treatment of 5% imiquimod cream, 2 treatments/week). (b) (4)

Please let me know if you have any questions.

Kind Regards,

Kelisha C. Turner
Regulatory Health Project Manager
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration

Tel: 301-796-0766
Fax: 301-796-9894
kelisha.turner@fda.hhs.gov

From: Sean Brennan [mailto:sean.brennan@gracewaypharma.com]
Sent: Friday, February 26, 2010 2:46 PM
To: Turner, Kelisha C
Cc: Owens, Margo
Subject: RE: NDA 22-483: Labeling - Calculation of Animal Multiples of Human Exposure (sections 8.1 and 13.1)

Dear Ms. Turner:

Reference is made to NDA 22-483 and to our complete response letter dated January 29, 2010. Reference is also made to your email response dated February 25, 2010 to our request (February 19, 2010) for additional information on the calculation of animal multiples of human exposures.

Thank you for clarifying how you calculated the MRHD ratios for Zyclara.

However, we request the following additional clarification.

3/18/2010

The Division responded:

(b) (4)

Table 11.4.4.1.2.F. Median AUC_{0n} Values (ng·hr/mL) Following Administration of the First Dose and the Last Dose During Week 16

BEST AVAILABLE
COPY

	Face (12.5 mg)		Scalp (25 mg)		Arms/Hands (75 mg)	
	First Dose	Last Dose	First Dose	Last Dose	First Dose	Last Dose
Overall	0.997 (n=18)	1.81 (n=19)	-	-	17.9 (n=23)	31.5 (n=17)
Males	1.11 (n=8)	1.26 (n=9)	1.33 (n=10)	3.87 (n=8)	18.4 (n=12)	25.6 (n=8)
Females	0.968 (n=10)	1.86 (n=10)	-	-	17.9 (n=11)	35.3 (n=9)

(b) (4)

If you would like to discuss this further or need additional information please contact me.

Sincerely,

Sean Brennan Ph.D.
Sr. VP, Regulatory Affairs
Graceway Pharmaceuticals, LLC

Office: 423-274-5210

From: Turner, Kelisha C [mailto:Kelisha.Turner@fda.hhs.gov]
Sent: Thursday, February 25, 2010 4:32 PM
To: Sean Brennan
Cc: Owens, Margo
Subject: RE: NDA 22-483: Labeling - Calculation of Animal Multiples of Human Exposure (sections 8.1 and 13.1)

Dear Dr. Brennan,

Please refer to your complete response dated January 29, 2010 for NDA 022483 Zyclara (imiquimod) Cream, 3.75%. Reference is also made to our draft labeling sent to you on February 19, 2010 and your email dated February 19, 2010

3/18/2010

containing your request for clarification of the calculations used in the animal multiples of human exposure as provided in the Use in Specific Populations and Nonclinical Toxicology sections of the labeling.

We have the following response to your request for clarification:

(b) (4)

Please let me know if you have any additional questions.

Kind Regards,

Kelisha C. Turner
Regulatory Health Project Manager
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration

3/18/2010

Tel: 301-796-0766
Fax: 301-796-9894
kelisha.turner@fda.hhs.gov

-----Original Message-----

From: Sean Brennan [mailto:sean.brennan@gracewaypharma.com]
Sent: Friday, February 19, 2010 1:06 PM
To: Turner, Kelisha C
Subject: NDA 22-483: Labeling - Calculation of Animal Multiples of Human Exposure (sections 8.1 and 13.1)

Dear Ms. Turner:

In the subject sections, the animal multiples of human exposure are shown and are quite different from those calculated by Graceway. In order for us to better understand these differences, we are asking for the reviewer to provide the method of calculation of these multiples. Also, a couple of example calculations would be helpful for our understanding.

Please contact me if you have additional questions.

Sincerely,

Sean Brennan Ph.D.
Graceway Pharmaceuticals, LLC

Office: 423-274-5210

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/

KELISHA C TURNER
03/18/2010

MEMORANDUM OF TELECON

DATE: March 1, 2010

APPLICATION NUMBER: NDA 022483, Zyclara (imiquimod) Cream, 3.75%.

BETWEEN:

Name: **Graceway Pharmaceuticals, LLC.**
Alicia Cabrelli, Regulatory Affairs
Jim Lee, M.D., Medical Affairs
Sharon Levy, M.D., Product Development
Robert Babilon, Product Development
Jason Wu, M.D., Product Development
Jim Kulp, Product Development

Phone: 1-866-212-0875 (call-in)

Representing: Graceway Pharmaceuticals, LLC.

AND

Name: **Division of Dermatology and Dental Products**
Tatiana Oussova, M.D., M.P.H., Deputy Director of Safety
Jill Lindstrom, M.D., Clinical Team Leader
Milena Lolic, M.D., Clinical Reviewer
Kelisha C. Turner, B.S., Regulatory Health Project Manager

SUBJECT: PMR language for NDA 022483 Zyclara (imiquimod) Cream, 3.75%

Background:

The Agency initiated a teleconference with the applicant to discuss draft PMR language for NDA 022483 Zyclara (imiquimod) Cream, 3.75%.

The Agency provided the applicant with the following draft PMR language in preparation for the teleconference:

Conduct a 2-way cross-over trial in subjects with actinic keratoses on the face to assess the potential of topical imiquimod to produce symptomatic arrhythmia. Zyclara 3.75% cream should be used as labeled, and event-monitoring via external event recorder with loop recording capability should be performed during all of the treatment phases (first and second 2-week treatment periods for both test articles).

The applicant stated that they would like to forward the discussion points to other Graceway members.

The applicant concurred with the Agency's draft language regarding population and the type of event monitoring. [REDACTED] (b) (4)

[REDACTED] the Agency expressed inclination toward use of the regimen proposed for labeling.

The Agency stated that our understanding is that the number of subjects [REDACTED] (b) (4) proposed in the protocol synopsis [REDACTED] (b) (4) was based on data regarding the change in heart rates, but that the focus of the study described in the Agency's draft language, would be the risk of imiquimod to cause symptomatic arrhythmias. The applicant asked what size study the Agency is considering. The Agency stated that we are considering a size of 200 subjects. The Agency thanked the applicant for their comments.

The call ended amicably.

Addendum:

On March 2, 2010, the applicant requested the information referenced by the Agency in regards to our basis for the study size estimates. In response, a list of references were provided to the applicant.

Jill Lindstrom, M.D.
Clinical Team Leader
Division of Dermatology and Dental Products
Center for Drug Evaluation and Research

Turner, Kelisha C

From: Turner, Kelisha C
Sent: Wednesday, March 03, 2010 2:44 PM
To: 'Alicia Cabrelli'
Cc: Owens, Margo; Sean Brennan
Subject: RE: NDA 22-483- Follow-Up Question to Telecon RE: PMR

Hi Alicia,

Please find the response to your question below:

Bass EB et al: The duration of Holter monitoring in patients with syncope. Is 24-hours enough? Arch Inter Med. 1990 May;150(5):1073-8
Gibson TC et al: Diagnostic efficacy of 24-hour electrocardiographic monitoring for syncope. Am J Cardiol. 1984 Apr 1;53(8):1013-7
Mason JW: A comparison of electrophysiologic testing with Holter monitoring to predict antiarrhythmic-drug efficacy for ventricular tachyarrhythmias. N Engl J Med. 1993 ;329:445-451
Krahn AD et al: Predicting the outcome of patients with unexplained syncope undergoing prolonged monitoring. PACE 2002;25:37-41
The ESVEM Investigators: The ESVM Trial. Circulation 1989;79:1354-1360

Please let me know if you have any questions.

Thank you.

Kelisha C. Turner
Regulatory Health Project Manager
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration

Tel: 301-796-0766
Fax: 301-796-9894
kelisha.turner@fda.hhs.gov

From: Alicia Cabrelli [mailto:alicia.cabrelli@gracewaypharma.com]
Sent: Tuesday, March 02, 2010 3:51 PM
To: Turner, Kelisha C
Cc: Owens, Margo; Sean Brennan
Subject: NDA 22-483- Follow-Up Question to Telecon RE: PMR

Dear Kelisha-

During today's teleconference, the reviewers stated references that they used for the 100 and 200 subject clinical study size estimates. Could you please provide us that information?

Thank you.

Regards,

Alicia

3/16/2010

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/

KELISHA C TURNER
03/18/2010

TATIANA OUSSOVA
03/18/2010

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO: CDER-DDMAC-RPM	FROM: (Name/Title, Office/Division/Phone number of requestor) Kelisha Turner, Regulatory Project Manager, 301-796-0766 Milena Lolic, MD, Clinical Reviewer, 301-796-3825 Jill Lindstrom, MD, Clinical Team Leader, 301-796-0944
------------------------------	------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

REQUEST DATE Feb. 25, 2010	IND NO.	NDA/BLA NO. 022483	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
-------------------------------	---------	-----------------------	-----------------------------------------------

NAME OF DRUG Zyclara (imiquimod) Cream, 3.75%	PRIORITY CONSIDERATION Class 1 Resubmission	CLASSIFICATION OF DRUG 5	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) March 2, 2010
-----------------------------------------------------	------------------------------------------------	-----------------------------	-------------------------------------------------------------------------------------------

NAME OF FIRM: Graceway Pharmaceuticals, LLC	PDUFA Date: March 29, 2010
------------------------------------------------	----------------------------

TYPE OF LABEL TO REVIEW

TYPE OF LABELING: (Check all that apply)	TYPE OF APPLICATION/SUBMISSION	REASON FOR LABELING CONSULT
<input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE (IFU)	<input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	<input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION

EDR link to submission: \\FDSWA150\nonectd\N22483\N_000\2010-01-29

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS: This submission is a Complete Response - Class 1 Resubmission. Please review the carton and container label, package insert and patient package insert for NDA 022483 Zyclara (imiquimod) Cream, 3.75%.

Labeling Meetings: March 2, 2010

Thank you.

SIGNATURE OF REQUESTER
Kelisha Turner
Milena Lolic, MD
Jill Lindstrom, MD

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> eMAIL <input type="checkbox"/> HAND

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/

KELISHA C TURNER
02/25/2010



Shari L. Targum, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993
Tel (301) 796-1151

Memorandum

DATE: February 23, 2010

FROM: Shari L. Targum, M.D., Team Leader
Division of Cardiovascular and Renal Drug Products, HFD-110

THROUGH: Norman Stockbridge, M.D., Ph.D., Director
Division of Cardiovascular and Renal Drug Products, HFD-110

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

SUBJECT: NDA 22-483

NAME OF DRUG: Imiquimod cream, 3.75%

TRADE NAME: Zyclara

FORMULATION: (b) (4)

RELATED APPLICATIONS: N/A

APPROVED INDICATIONS: N/A

SPONSOR: Graceway Pharmaceuticals, LLC

DOCUMENTS AVAILABLE FOR REVIEW: 1. Consult request; 2. NDA 22-483 (edr) 12/24/2008;
3. prior Cardio-Renal and TQT consultations.

DATE CONSULT RECEIVED: February 5, 2010

DESIRED COMPLETION DATE: February 27, 2010

DATE CONSULT COMPLETED: February 22, 2010

REASON FOR CONSULTATION:

This Division has been asked to review the complete response to NDA 022-483 Zyclara (imiquimod) cream, 3.75%, and comment on the following:

1. Is the number of subjects for the (b) (4) study sufficient to detect change in heart rate and rhythm (in particular to detect arrhythmias such as supraventricular tachycardia or ventricular tachycardia)?
2. Is the duration and frequency of Holter monitoring adequate to capture imiquimod impact on heart rate and cardiac rhythm?
3. Will the protocol as drafted adequately address the question of topical imiquimod effects on heart rate and rhythm?

BACKGROUND:

Imiquimod is a toll-like receptor (TLR) agonist. Although its mechanism of action is not elucidated, imiquimod appears to mediate its effects via activation of TLR7. Imiquimod 5% cream was initially approved for marketing in 1997; current indications include: clinically typical, nonhyperkeratotic,

nonhypertrophic actinic keratoses on the face or scalp (immunocompetent adults); superficial basal cell carcinoma; and external genital and perianal warts/condyloma acuminata.

The sponsor is seeking approval for a 3.75% strength cream with a new dosing regimen (more frequent application to a larger surface area) for the treatment of actinic keratoses.

On 10/16/2009, the Agency issued a Complete Response letter, which included the following deficiencies: 1. Electrocardiographic studies were not conducted during development of this formulation and the effect of imiquimod on cardiac repolarization and arrhythmias is unknown; 2. Unknown comparative bioavailability of Zyclara and Aldara (used as labeled). The Division requested that the sponsor conduct a thorough QT study with Holter monitoring to evaluate the effect of Zyclara on cardiac repolarization and heart rate.

On 12/16/2009, the sponsor requested a formal dispute resolution concerning the Division's decision to require a thorough QT study prior to approval; the sponsor has agreed to conduct the study post-approval. On 1/25/2010, the Office Director granted the sponsor's request that the requirement for a pre-approval thorough QT study be waived.

(b) (4)

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/

SHARI L TARGUM
02/23/2010

NORMAN L STOCKBRIDGE
02/23/2010



NDA 022483

ACKNOWLEDGE CLASS 1 COMPLETE RESPONSE

Graceway Pharmaceuticals, LLC
Attention: Sean Brennan, Ph.D.
Vice President, Regulatory Affairs
340 Martin Luther King Jr. Blvd., Suite 300
Bristol, TN 37620

Dear Dr. Brennan:

We acknowledge receipt on January 29, 2010 of your January 29, 2010 resubmission to your new drug application for Zyclara (imiquimod) Cream, 3.75%.

We consider this a complete, class 1 response to our October 16, 2009 action letter. Therefore, the user fee goal date is March 29, 2010.

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

Sincerely,

{See appended electronic signature page}

Kelisha C. Turner
Regulatory Project Manager
Division of Dermatology and Dental
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/

KELISHA C TURNER
02/10/2010



NDA 022483

INFORMATION REQUEST

Graceway Pharmaceuticals, LLC
Attention: Sean Brennan, Ph.D.
Vice President, Regulatory Affairs
340 Martin Luther King Jr. Blvd., Suite 300
Bristol, TN 37620

Dear Dr. Brennan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyclara (imiquimod) Cream, 3.75%.

We also refer to your January 29, 2010 submission, containing your response to our Complete Response letter dated October 16, 2009.

We are reviewing the Clinical and CMC sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Clinical:

Provide the following information about the subject 01/210 from study GW01-0702:

1. Date when the syncope/car accident occurred
2. Dates when Holter monitoring was utilized (from-until)
3. Date of occurrence of nonsustained VT that was captured during Holter monitoring

CMC:

Amend the presentation of your dosage form and strength on all container/closure systems as follows and provide the color mock-ups.

Zyclara
(Imiquimod) Cream
3.75%

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

Sincerely,

{See appended electronic signature page}

Margo Owens
Project Management Team Leader
Division of Dermatology and Dental
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/

MARGO L OWENS
02/06/2010

REQUEST FOR CONSULTATION

TO (Office/Division): **Division of Cardiovascular and Renal Products (Cardiology)**
Devi Kozeli, Project Manager

FROM (Name, Office/Division, and Phone Number of Requestor):
Division of Dermatology and Dental Products
Milena Lolic, M.D. 301-796-3825
Jill Lindstrom, M.D., Team Leader 301-796-0944
Kelisha Turner, Regulatory Project Manager
301-796-0766

DATE
February 5, 2010

IND NO.

NDA NO.
022483

TYPE OF DOCUMENT
Complete Response -
Class 1 Resubmission

DATE OF DOCUMENT
January 29, 2010

NAME OF DRUG
Zyclara (imiquimod) Cream,
3.75%

PRIORITY CONSIDERATION
Class 1 Resubmission

CLASSIFICATION OF DRUG
5

DESIRED COMPLETION DATE
February 18, 2010

NAME OF FIRM: Graceway Pharmaceuticals, LLC.

REASON FOR REQUEST

I. GENERAL

- | | | |
|----------------------------------------------------------|--------------------------------------------------|------------------------------------------------------------|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input checked="" type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|-------------------------------------------------|-------------------------------------------------|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--------------------------------------------------|------------------------------------------------------|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: The complete response to NDA 022483 Zyclara (imiquimod) Cream, 3.75% is available electronically at \\FDSWA150\nonectd\N22483\N_000\2010-01-29. Please review and comment on the following:

1. Is the number of subjects for the (b) (4) study sufficient to detect change in heart rate and rhythm (in particular to detect the arrhythmias such as SVT or VT)?
2. Is the duration of Holter monitoring and frequency of Holter monitoring adequate to capture imiquimod impact on heart rate and cardiac rhythm ?
3. Will the protocol as drafted adequately address the question of topical imiquimod effects on heart rate and rhythm?

SIGNATURE OF REQUESTOR Milena Lolic, M.D. Jill Lindstrom, M.D. Kelisha Turner		METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND	
PRINTED NAME AND SIGNATURE OF RECEIVER		PRINTED NAME AND SIGNATURE OF DELIVERER	

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/

KELISHA C TURNER

02/05/2010

REQUEST FOR CONSULTATION

TO (Office/Division): **Division of Cardiovascular and Renal Products (TQT)**
Devi Kozeli, Project Manager

FROM (Name, Office/Division, and Phone Number of Requestor):
Division of Dermatology and Dental Products
Milena Lolic, M.D. 301-796-3825
Jill Lindstrom, M.D., Team Leader 301-796-0944
Kelisha Turner, Regulatory Project Manager
301-796-0766

DATE
February 5, 2010

IND NO.

NDA NO.
022483

TYPE OF DOCUMENT
Complete Response -
Class 1 Resubmission

DATE OF DOCUMENT
January 29, 2010

NAME OF DRUG
Zyclara (imiquimod) Cream,
3.75%

PRIORITY CONSIDERATION
Class 1 Resubmission

CLASSIFICATION OF DRUG
5

DESIRED COMPLETION DATE
February 18, 2010

NAME OF FIRM: Graceway Pharmaceuticals, LLC.

REASON FOR REQUEST

I. GENERAL

- | | | |
|----------------------------------------------------------|--------------------------------------------------|------------------------------------------------------------|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input checked="" type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|-------------------------------------------------|-------------------------------------------------|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--------------------------------------------------|------------------------------------------------------|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: The complete response to NDA 022483 Zyclara (imiquimod) Cream, 3.75% is available electronically at \\FDSWA150\nonectd\N22483\N_000\2010-01-29. Please review and comment on the following:

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

SIGNATURE OF REQUESTOR Milena Lolic, M.D. Jill Lindstrom, M.D. Kelisha Turner		METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND	
PRINTED NAME AND SIGNATURE OF RECEIVER		PRINTED NAME AND SIGNATURE OF DELIVERER	

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/

KELISHA C TURNER
02/05/2010



NDA 022483

DISPUTE APPEAL - RESPONSE

Graceway Pharmaceuticals, LLC
Attention:
Jefferson J. Gregory, B.S. Pharm., J.D., H.D.
Chairman and Chief Executive Officer
340 Martin Luther King Jr. Blvd.
Suite 500
Bristol, TN 37620

Dear Mr. Gregory:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyclara (imiquimod) Cream, 3.75%.

We refer also to your December 16, 2009, request for formal dispute resolution concerning the requirement to conduct a thorough QT study prior to approval of your NDA.

I have reviewed the administrative record and have had discussions with the NDA review team, including staff from the Division of Dermatology and Dental Products (DDDP), the Division of Clinical Pharmacology III, the QT/Interdisciplinary Review Team (in the Division of Cardiovascular and Renal Products, DCRP), and the Office of Surveillance and Epidemiology (OSE) who are familiar with this application. Your request that the requirement for a pre-approval thorough QT study be waived is granted.

On October 16, 2009, the Division of Dermatology and Dental Products (DDDP) issued a complete response letter for NDA 022483. The letter stated that "in the absence of adequate information about the comparative bioavailability of Zyclara relative to Aldara and adequate data demonstrating that Zyclara does not affect cardiac repolarization, the potential risks of Zyclara are not justified by the potential benefits to patients with actinic keratoses of the face or scalp". DDDP requested that Graceway conduct a thorough QT study with Holter monitoring to demonstrate the impact of Zyclara on cardiac repolarization and heart rate.

Following receipt of the complete response letter, Graceway requested and was granted a Type A (post-action) meeting with DDDP, held on November 17, 2009. Staff from DDDP and OSE attended the meeting. Graceway's meeting package referred to several clinical studies of oral, subcutaneous and topical imiquimod in which ECG monitoring had been performed. Of note, study R-837-009, an oral dose escalation and safety study, included pharmacokinetic sampling. These studies had been submitted to the Aldara NDA but were not specifically referenced in the

Zyclara NDA¹ as Graceway understood from discussions at the October 29, 2008 pre-NDA meeting that DDDP would assess systemic exposure levels of imiquimod to determine its potential for cardiac repolarization. Graceway, therefore assumed that ECG data were not needed.

At the post-action meeting, DDDP informed Graceway that the previously conducted studies were not submitted to NDA 22-483, and therefore the Division could not agree that resubmission of the data from those studies would be sufficient to address the impact of imiquimod on cardiac repolarization.² This prompted your current request for formal dispute resolution.

My comments will focus on several issues that Graceway raised at the November 17, 2009 post-action meeting and subsequently in your December 16, 2009 appeal. Because Graceway did not specifically reference study R-837-009 and other clinical imiquimod studies in which ECG monitoring was performed, I could not consider them in my decision regarding the need for a pre-approval thorough QT study, the subject of this formal appeal.³ My decision is based on the merits of Graceway's other arguments.

A. Prior regulatory history for topical imiquimod

Zyclara (imiquimod) Cream, 3.75% (NDA 022483), is a lower strength of Graceway's Aldara (imiquimod) Cream, 5% (NDA 020723) proposed for the treatment of actinic keratosis involving the face and balding scalp in immunocompetent adults (AK). The proposed regimen is daily application for two weeks, followed by a two-week no treatment period, and a second two-week treatment period. Aldara was originally approved on February 27, 1997, for the treatment of external genital and perianal warts/condyloma acuminata in patients 12 years of age or older (EGW). In 2004, Aldara was approved for the topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic AK on the face and scalp in immunocompetent adults; the approved regimen is twice weekly application for 16 weeks. Aldara was also approved in 2004 for the topical treatment of biopsy-confirmed, primary superficial basal cell carcinoma in immunocompetent adults (sBCC).

Graceway points to several regulatory actions, including the above-mentioned approvals, and discussions with FDA related to topical imiquimod in which no concerns were raised by FDA regarding the potential for cardiac repolarization or the need for a thorough QT study. Below is a summary of FDA's activities as they relate to the assessment of, or concerns about, cardiac repolarization based on my review of available documents and discussions with team members.

Regarding Aldara, the approval letter for the original application in 1997 and the approval letters for the two supplemental applications in 2004 did not specify any postmarketing commitments designed to study the effect of imiquimod on cardiac repolarization. Although the regimen for sBCC was more dose intense (applications 5 times per week versus 2 times per week for AK or 3

¹ See clarification provided by Graceway via email on December 24, 2009.

² See Memorandum of Meeting Minutes from Type A Meeting held on November 17, 2009, under "Meeting Discussion," p.4,

³ On December 30, 2009, I informed Dr. Sean Brennan of Graceway via teleconference that I could not consider the previously conducted studies with ECG monitoring in this appeal.

times per week for EGW), the clinical reviewers were not particularly concerned about the possibility of increased systemic exposure since the area of application was limited to a single sBCC lesion. The approval letter for the AK indication did specify studies to be conducted in areas other than the face and scalp, for longer durations and involving areas larger than 25 cm²; pharmacokinetic evaluation of a subset of patients was to be conducted, but no request was made for ECG measurements.

On March 17, 2005, DDDP requested that the Aldara sponsor (3M Pharmaceuticals⁴) submit a comprehensive summary of postmarketing adverse event reports suggestive of systemic effects, including cardiac, neuropsychiatric, hepatic and endocrine adverse events, and propose appropriate labeling. The sponsor's analysis was consistent with that of OSE (formerly Office of Drug Safety or ODS). On August 9, 2005, changes to the product label were approved that included the addition of a **Postmarketing Experience** subsection under **ADVERSE REACTIONS**. This revision added several adverse reactions, including the following under the *Cardiovascular* heading: capillary leak syndrome, cardiac failure, cardiomyopathy, pulmonary edema, arrhythmias (tachycardia, atrial fibrillation, palpitations), chest pain, ischemia, myocardial infarction, and syncope. As these reactions were reported voluntarily, the label states that "it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure". A subsequent analysis of spontaneous adverse events by OSE dated August 12, 2009, did not identify any new postmarketing safety signals and no further labeling enhancements were recommended.

Regarding Zyclara, the minutes of two meetings held to discuss that product's development program⁵ include a general statement advising Graceway to "address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14)". The minutes of these meetings do not reflect any specific discussions, agreements reached, or action items with respect to QT studies. In a third meeting, the pre-NDA meeting held on October 29, 2008, Graceway specifically asked whether FDA agreed that no additional data were needed to address the potential for QT/QTc prolongation with Zyclara use. FDA's response was that Graceway "provide data to support that the 3.75% has less systemic exposure than the 5% as used in the study 1520-IMIQ. A determination...will be based on the adequacy of those data," and, "Refer to the E14 guidance document."

Thus, the requisite comparison from DDDP's perspective appears to have been between the proposed regimen for Zyclara (2 packets of 3.75% cream or 18.75 mg daily to full face and scalp for two 2-week courses separated by a 2-week break) and the dosing regimen in 1520-IMIQ (up to 6 packets of 5% cream or 75 mg applied twice a week to the head, torso or extremities for up to three 16-week cycles). A comparison of Zyclara to Aldara as labeled was not specifically requested. Although a general reference is made to the E14 guidance, no specific discussion regarding the need for ECG measurement in clinical studies or conduct of specific studies to assess effects on the QT interval was captured in the meeting minutes. The E14 guidance is concerned primarily with the development of novel agents with systemic bioavailability, and

⁴ On December 29, 2006, Graceway Pharmaceuticals, LLC, acquired 3M's Aldara Cream, 5%.

⁵ A guidance meeting to discuss the AK indication was held on October 31, 2007; an End-of-Phase 2 meeting to discuss the EGW indication was held on January 20, 2008.

new doses or new routes of administration that result in significantly higher systemic exposures. I believe that DDDP's response at the pre-NDA meeting could have been interpreted as meaning that Graceway could address the risk of cardiac repolarization primarily on pharmacokinetic grounds. The E14 guidance would apply only if significantly higher exposures were found with the new dosing regimen. However, in my recent discussions with DDDP conducted to review this appeal I learned that, in fact, *any* systemic exposure would be viewed as a trigger for the need for ECG evaluation, at a minimum, if not a thorough QT study, during the clinical development program. (See section B below.)

Upon receipt of the Zyclara NDA, DDDP's filing communication letter dated March 2, 2009, requested "data to address the potential of the product to affect cardiac repolarization". Graceway responded with pharmacokinetic arguments. DDDP did not respond further as to the adequacy of this response or specifically request ECG data to complete its review.

Lastly, it should be pointed out that with the enactment of the Food and Drug Administration Amendments Act of 2007 (FDAAA), Section 505(o) of the Federal Food, Drug, and Cosmetic Act states that FDA can require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes if FDA makes certain findings required by the statute (section 505(o)(3)(A)). To my knowledge, FDA has not made such a finding with respect to Aldara since FDAAA went into effect on March 25, 2008.

B. Systemic exposures to imiquimod and concerns regarding cardiac repolarization

Zyclara at maximal use conditions (i.e., 2 packets or 18.75 mg daily over the full face and scalp for 3 weeks, as evaluated in study GW01-0706) results in mean peak serum imiquimod levels of 0.323 ± 0.159 ng/mL at day 21; the highest concentration observed was 0.588 ng/mL. Graceway believes that the risk of a clinically meaningful QT effect with these low exposures is non-existent. For imiquimod to exhibit a QT prolonging effect at these concentrations it would need to be an extremely potent proarrhythmic drug.

In a consult dated September 15, 2009, the DCRP QT/IRT stated that "A key question is whether the new formulation will lead to an increase in systemic exposure compared to the old formulation... If the new formulation will lead to the potential of higher systemic exposures..." a case could be made for additional testing, such as a thorough QT study. In recent discussions held to address this appeal, the DCRP QT/IRT clarified that, in their experience, no product with exposures this low has been associated with effects on cardiac repolarization. This experience, taken together with the apparent lack of effect on cardiac repolarization in analyses of ECG data submitted from oral imiquimod exposure in the Type A meeting package, lead the DCRP QT/IRT to conclude that imiquimod cream offers minimal risk to delay cardiac repolarization. Further, the DCRP QT/IRT does not recommend that a thorough QT study be conducted, although some amount of ECG monitoring in the clinical development program would have been desirable. DDDP acknowledges this revised recommendation. Further internal discussion regarding the cardiac repolarization risks of small molecules with low systemic exposures is planned, including guidance development regarding appropriate monitoring in clinical trials evaluating such products.

C. Comparative systemic exposures and clinical safety of Zyclara and Aldara

The table below summarizes systemic exposures at steady state following maximal use application of Zyclara or Aldara in AK patients. These regimens exceed recommended dosing with respect to the number of packets applied, frequency or duration of treatment. The results for study 1402-IMIQ are already labeled.

Graceway notes that a comparison of the Aldara and Zyclara pharmacokinetic profiles in these studies shows that Zyclara falls within peak levels seen with Aldara. In addition, even with the higher exposures in 1520-IMIQ, a study of the application of up to six packets of Aldara 3 times weekly for up to three 16-week cycles in 551 subjects⁶, no new safety concerns, including cardiac safety, were observed.

At the October 2008 pre-NDA meeting, FDA’s response to Clinical/Biostatistics Question 9 regarding whether 1520-IMIQ could be considered sufficient to meet the requirement of long-term safety of the 3.75% imiquimod cream formulation was “provide data to support that the 3.75% has less systemic exposure than the 5% as used in study 1520-IMIQ”. This would suggest DDDP’s willingness to “bracket” the exposures with Zyclara by considering data from suprathreshold exposures to Aldara.

	C_{max} (ng/mL)		AUC (ng hr/mL)	
	Mean (SD)	Ratio^a	Mean (SD)	Ratio^a
Zyclara GW01-0706 2pkts (18.75 mg) daily to face/scalp for 3 wks	0.323 (0.159)		5.97 (3.09)	
Aldara 1520-IMIQ 6 pkts (75 mg) 2x/wk to > 25% BSA for 16 wks	0.958 (1.18)	2.96	24.3 (26.9)	4.07
Aldara 1402-IMIQ (16 wks)				
1 pkt (12.5) 3x/wk to face	0.120 (0.063)	0.37	2.06 (1.70)	0.34
2 pkts (25 mg) 3x/wk to scalp	0.214 (0.097)	0.66	4.89 (4.41)	0.82
6 pkts (75 mg) 3x/wk to hands/forearms	3.53 (6.52)	10.92	55.4 (76.0)	9.27

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⁶ 1520-IMIQ is a long-term safety and pharmacokinetic study conducted as a postmarketing commitment negotiated at the time of the approval of the AK indication. Study results were submitted to both Aldara and Zyclara NDAs.

In his review of the NDA, the clinical pharmacology reviewer noted that Aldara exposures in 1402-IMIQ “book-end” those seen with Zyclara. In their reviews, the DDDP clinical reviewers did not find the suprathreshold exposures in the Aldara studies reassuring as no ECG monitoring had been performed in these studies. In addition, they raised concerns regarding three spontaneous reports of tachycardia⁷ and one report of unexplained death in the postmarketing experience with Aldara, a case of nonsustained ventricular tachycardia in Zyclara study GW01-0702, the absence of ECG monitoring in the Zyclara clinical development program, and the absence of any ECG data submitted in the Zyclara NDA. Thus, the clinical reviewers limited their cross-study comparisons to those between Zyclara in GW01-0706 (with a mean C_{max} of 0.323 ng/mL) and Aldara as evaluated in the two lower exposure cohorts of 1402-IMIQ (with a mean C_{max} of 0.120 ng/mL and 0.214 ng/mL, respectively). These comparisons lead to the conclusion that Zyclara may result in greater systemic exposure than Aldara when used as labeled. This sentiment, in turn, is reflected in the complete response letter.

Notwithstanding the intersubject variability observed in the pharmacokinetic studies, and the inherent limitations of cross-study comparisons of adverse events reported in association with a daily 2-week regimen versus a twice weekly 16-week regimen, I believe the available data support the following:

- Systemic imiquimod exposure with maximal use of Zyclara for 3 weeks (mean C_{max} of 0.323 ng/mL) is sufficiently bracketed by the imiquimod exposures seen with maximal use of Aldara in 1402-IMIQ and 1520-IMIQ.
- The safety profile of Zyclara administered daily for 2 weeks in clinical trials approximates that of Aldara as labeled for the treatment of AK [REDACTED] ^{(b) (4)} for 16 weeks) in terms of treatment-emergent adverse events and application site reactions. Local skin reactions were more frequent with Zyclara use in terms of edema, erosion and exudate, but not in terms of erythema, flaking or scabbing.
- The safety profile of Zyclara administered daily for 2 weeks approximates that of Aldara when administered to AK patients with head involvement of 200 cm² in doses of 12.5 to 75 mg twice weekly for 16 weeks/cycle, for up to three treatment cycles (1520-IMIQ) in terms of treatment-emergent adverse events and application site reactions. Local skin reactions were more frequent with Zyclara use in terms of edema and exudate, but not in terms of erythema, erosion, flaking or scabbing.

Thus, in accordance with DDDP’s advice provided to Graceway at the pre-NDA meeting, these data taken together support the short- and long-term safety of Zyclara.

D. Reports suggestive of proarrhythmic potential

Graceway contends that in its 13-year postmarketing experience, cardiac repolarization has not been attributed to Aldara use. At the post-action meeting, discussion ensued regarding three positive rechallenge postmarketing reports (one of symptomatic SVT and two others of

⁷ A positive rechallenge case involving documented symptomatic SVT was reported in a 44 year old man using Aldara 3 times weekly for sBCC; two additional positive rechallenge cases involving a 34 year old woman and a 14 year old boy using Aldara for EGW and common warts, respectively, had no ECG information.

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As part of the review of the Zyclara NDA, DDDP consulted the DCRP QT/IRT. A consult dated May 28, 2009, re-reviewed the findings from the ODS consult of 2005 which identified 12 cardiac adverse events out of a total of 1366 reports (raw count), including seven cases of arrhythmia. The DCRP QT/IRT agreed with the ODS assessment that although the contribution of topical imiquimod could not be conclusively ruled out, these cases were confounded by advanced age and co-morbidities. In a consult dated September 15, 2009, DCRP was asked to comment on the proarrhythmic potential of imiquimod. The reviewer concluded that the available clinical information from spontaneous reports was scant and did not allow for definitive conclusions.

MGPS data mining analyses of the AERS database related to reports of QT prolongation, thromboembolism and myocardial ischemia were conducted by the DCRP QT/IRT on May 7, 2009. These analyses revealed that the incidence of these events among imiquimod users was similar to or less than the background rates in the general population. A repeat datamining analysis conducted on December 17, 2009 of AERS reports of arrhythmias (including conduction defects), congestive heart failure, coronary artery disease and events related to QT prolongation provided a similar result.

Following discussions with the DCRP QT/IRT held to address this appeal, I agree with Graceway that the spontaneous reports of undocumented tachycardia and symptomatic SVT are likely unrelated to any potential effects of imiquimod on the QT interval, which as stated above are not anticipated given the low systemic exposures associated with topical imiquimod use. Of the three reports of tachycardia, only that involving the report of symptomatic SVT has sufficient documentation to be compelling. The other two reports had no ECG documentation. The spontaneous report of unexplained death lacks sufficient clinical detail to assess, and the study report of post-exposure syncope lacks a temporal relationship to imiquimod application (occurring well after any systemic exposure would be expected) and is confounded by co-morbidities.

E. Standard for new drug approval

Graceway indicates that at the November 17, 2009 post-action meeting, DDDP implied that a higher safety bar was required for Zyclara because a) the product does not offer a new indication or treat a new patient population, and b) AK is not a serious or life-threatening condition and many treatment modalities are available.

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conditions suggest that the novelty or seriousness of the proposed indication would dictate drug approval or non-approval. Approval would be withheld if FDA determines that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.

F. Conclusions and Recommendations

First, regarding the subject of this formal dispute resolution, that is, the need for a pre-approval thorough QT study, I have considered a) the determinations by FDA (in 1997 and 2004) that the benefits of Aldara treatment outweigh its risks, b) the determination (in 2005) that labeling of several postmarketing spontaneous adverse events, including cardiovascular events, and continued pharmacovigilance was an acceptable means by which to ensure that the benefits of treatment continued to outweigh the risks, and c) the limited clinical information available regarding a few highly confounded case reports suggestive of proarrhythmic potential. I have also considered the available pharmacokinetic information for Aldara and Zyclara, and acknowledge both the limitations of cross-study comparisons and the intersubject variability observed in pharmacokinetic assessments. I have also considered the adverse event profiles for Aldara as labeled and with maximal use, and for Zyclara as studied in controlled clinical trials, again acknowledging the limitations of such comparisons. Taken together, I am persuaded that systemic imiquimod exposure with maximal use of Zyclara is sufficiently bracketed by the imiquimod exposures seen with maximal use of Aldara, and that these exposures are sufficiently low to provide reassurance that topical imiquimod offers minimal risk with regard to cardiac repolarization. In addition, Zyclara is intended for a patient population with AK that is analogous to that for Aldara, not a population at greater potential risk for cardiovascular adverse events. Therefore, I conclude that, with regard to NDA 022483, a thorough QT study is not needed pre-approval.

Second, recent discussions involving DDDP and consulting groups have taken place to consider a path forward for NDA 022483 and what further study might be warranted post-approval. The DCRP QT/IRT has reviewed the ECG data from R-837-009 submitted in the post-action meeting package, and considering the subnanomolar systemic exposure with topical imiquimod, is sufficiently reassured that a thorough QT study is not needed. Further, the DCRP QT/IRT has advised that a thorough QT study is not an efficient means to assess symptomatic tachyarrhythmias, such as SVT. Existing data may address the potential for imiquimod to trigger symptomatic tachyarrhythmias and should be submitted for review as described below.

Graceway should, therefore, submit a complete response to its October 16, 2009 complete response letter to include the following:

- proposed product labeling;
- a safety update that includes:
 - the full study report for R-837-009, including ECG tracings; and
 - information to address the possibility that imiquimod may trigger symptomatic tachyarrhythmias, such as SVT. This information should include a) a review of the clinical trial safety database for an imbalance of adverse events such as syncope, palpitations and dizziness for imiquimod compared to placebo, and b) an assessment of

- available data on heart rate (e.g., change from baseline and outlier analysis by dose/concentration); and
- a draft protocol synopsis for a postmarketing controlled clinical trial designed to assess the affects of topical imiquimod on heart rhythm.

This submission will be considered a Class 1 resubmission and will be reviewed on a two-month clock.

If you wish to pursue further appeal on this issue, submit a new request for formal dispute resolution to Amy Bertha, Dispute Resolution Project Manager.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22483	GI-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/

JULIE G BEITZ
01/15/2010



DATE: January 15, 2010

FROM: Julie Beitz, MD
Director, Office of Drug Evaluation III,
Office of New Drugs

SUBJECT: Formal dispute resolution request for Zyclara (imiquimod) cream 3.75%
NDA 022483

I. Background

Zyclara (imiquimod) Cream, 3.75% (NDA 022483), is a lower strength of Graceway Pharmaceutical's Aldara (imiquimod) Cream, 5% (NDA 020723) proposed for the treatment of actinic keratosis involving the face and balding scalp in immunocompetent adults (AK). The proposed regimen is daily application for two weeks, followed by a two-week no treatment period, and a second two-week treatment period. Aldara was originally approved on February 27, 1997, for the treatment of external genital and perianal warts/condyloma acuminata in patients 12 years of age or older (EGW). In 2004, Aldara was approved for the topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic AK on the face and scalp in immunocompetent adults; the approved regimen is twice weekly application for 16 weeks. Aldara was also approved in 2004 for the topical treatment of biopsy-confirmed, primary superficial basal cell carcinoma in immunocompetent adults (sBCC).

On October 16, 2009, the Division of Dermatology and Dental Products (DDDP) issued a complete response letter for NDA 022483. The letter stated that "in the absence of adequate information about the comparative bioavailability of Zyclara relative to Aldara and adequate data demonstrating that Zyclara does not affect cardiac repolarization, the potential risks of Zyclara are not justified by the potential benefits to patients with actinic keratoses of the face or scalp". DDDP requested that Graceway conduct a thorough QT study with Holter monitoring to demonstrate the impact of Zyclara on cardiac repolarization and heart rate. On December 16, 2009, Graceway requested a formal dispute resolution concerning DDDP's decision to require a thorough QT study for Zyclara prior to marketing approval. Graceway has committed to conducting the study post-approval.

Following receipt of the complete response letter, Graceway requested and was granted a Type A (post-action) meeting with DDDP, held on November 17, 2009. Staff from DDDP and the Office of Surveillance and Epidemiology (OSE) attended the meeting. The sponsor's meeting package referred to several clinical studies of oral, subcutaneous and topical imiquimod in which ECG monitoring had been performed. Of note, study R-837-009, an oral dose escalation and safety study, included pharmacokinetic sampling. These studies had been submitted to the Aldara NDA but were not specifically referenced in the Zyclara NDA¹ as Graceway understood from discussions at the October 29, 2008 pre-NDA meeting that DDDP would assess systemic

¹ See clarification provided by Graceway via email on December 24, 2009.

exposure levels of imiquimod to determine its potential for cardiac repolarization. Graceway, therefore assumed that ECG data were not needed.

At the post-action meeting, DDDP informed Graceway that the previously conducted studies were not submitted to NDA 22-483, and therefore the Division could not agree that resubmission of the data from those studies would be sufficient to address the impact of imiquimod on cardiac repolarization.² This prompted Graceway's current request for formal dispute resolution.

I have reviewed the administrative record and have had discussions with the NDA review team, including staff from the DDDP, Division of Clinical Pharmacology III, the QT/ Interdisciplinary Review Team (in the Division of Cardiovascular and Renal Products, DCRP), and OSE who are familiar with this application. Graceway's request that the requirement for a pre-approval thorough QT study be waived is granted.

My comments will focus on several issues that Graceway raised at the November 17, 2009 post-action meeting and subsequently in their December 16, 2009 appeal. Because Graceway did not specifically reference study R-837-009 and other clinical studies in which ECG monitoring was performed, I could not consider them in my decision regarding the need for a pre-approval thorough QT study, the subject of this formal appeal.³ My decision is based on the merits of Graceway's other arguments.

A. Prior regulatory history for topical imiquimod

Graceway points to several regulatory actions and discussions with FDA related to topical imiquimod in which no concerns were raised by FDA regarding the potential for cardiac repolarization or the need for a thorough QT study. These actions include the original Aldara approval in 1997, approval of two additional indications in 2004 and finalization of a pediatric Written Request in 2006 for Aldara, and more recent discussions with FDA regarding the clinical development program for Zyclara.

Below is a summary of FDA's activities as they relate to the assessment of, or concerns about, cardiac repolarization based on my review of available documents and discussions with team members.

Regarding Aldara, the approval letter for the original application in 1997 and the approval letters for the two supplemental applications in 2004 did not specify any postmarketing commitments designed to study the effect of imiquimod on cardiac repolarization. Although the regimen for sBCC was more dose intense (applications 5 times per week versus 2 times per week for AK or 3 times per week for EGW), the clinical reviewers were not particularly concerned about the possibility of increased systemic exposure since the area of application was limited to a single sBCC lesion. The approval letter for the AK indication did specify studies to be conducted in areas other than the face and scalp, for longer durations and involving areas larger than 25 cm²;

² See Memorandum of Meeting Minutes from Type A Meeting held on November 17, 2009, under "Meeting Discussion," p.4,

³ On December 30, 2009, I informed Dr. Sean Brennan of Graceway via teleconference that I could not consider the previously conducted studies with ECG monitoring in this appeal.

pharmacokinetic evaluation of a subset of patients was to be conducted, but no request was made for ECG measurements.

On March 17, 2005, DDDP requested that the Aldara sponsor (3M Pharmaceuticals⁴) submit a comprehensive summary of postmarketing adverse event reports suggestive of systemic effects, including cardiac, neuropsychiatric, hepatic and endocrine adverse events, and propose appropriate labeling. The sponsor's analysis was consistent with that of OSE (formerly Office of Drug Safety or ODS). On August 9, 2005, changes to the product label were approved that included the addition of a **Postmarketing Experience** subsection under **ADVERSE REACTIONS**. This revision added several adverse reactions, including the following under the *Cardiovascular* heading: capillary leak syndrome, cardiac failure, cardiomyopathy, pulmonary edema, arrhythmias (tachycardia, atrial fibrillation, palpitations), chest pain, ischemia, myocardial infarction, and syncope. As these reactions were reported voluntarily, the label states that "it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure". A subsequent analysis of spontaneous adverse events by OSE dated August 12, 2009, did not identify any new postmarketing safety signals and no further labeling enhancements were recommended.

Regarding Zyclara, the minutes of two meetings held to discuss that product's development program⁵ include a general statement advising Graceway to "address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14)". The minutes of these meetings do not reflect any specific discussions, agreements reached, or action items with respect to QT studies. In a third meeting, the pre-NDA meeting held on October 29, 2008, Graceway specifically asked whether FDA agreed that no additional data were needed to address the potential for QT/QTc prolongation with Zyclara use. FDA's response was that Graceway "provide data to support that the 3.75% has less systemic exposure than the 5% as used in the study 1520-IMI. A determination...will be based on the adequacy of those data," and, "Refer to the E14 guidance document."

Thus, the requisite comparison from DDDP's perspective appears to have been between the proposed regimen for Zyclara (2 packets of 3.75% cream or 18.75 mg daily to full face and scalp for two 2-week courses separated by a 2-week break) and the dosing regimen in 1520-IMI (up to 6 packets of 5% cream or 75 mg applied twice a week to the head, torso or extremities for up to three 16-week cycles). A comparison of Zyclara to Aldara as labeled was not specifically requested. Although a general reference is made to the E14 guidance, no specific discussion regarding the need for ECG measurement in clinical studies or conduct of specific studies to assess effects on the QT interval was captured in the meeting minutes. The E14 guidance is concerned primarily with the development of novel agents with systemic bioavailability, and new doses or new routes of administration that result in significantly higher systemic exposures. I believe that DDDP's response at the pre-NDA meeting could have been interpreted as meaning that Graceway could address the risk of cardiac repolarization primarily on pharmacokinetic grounds. The E14 guidance would apply only if significantly higher exposures were found with the new dosing regimen. However, in my recent discussions with DDDP conducted to review this appeal I learned that, in fact, *any* systemic exposure would be viewed as a trigger for the

⁴ On December 29, 2006, Graceway Pharmaceuticals, LLC, acquired 3M's Aldara Cream, 5%.

⁵ A guidance meeting to discuss the AK indication was held on October 31, 2007; an End-of-Phase 2 meeting to discuss the EGW indication was held on January 20, 2008.

need for ECG evaluation, at a minimum, if not a thorough QT study, during the clinical development program. (See section B below.)

Upon receipt of the Zyclara NDA, DDDP's filing communication letter dated March 2, 2009, requested "data to address the potential of the product to affect cardiac repolarization". Graceway responded with pharmacokinetic arguments. DDDP did not respond further as to the adequacy of this response or specifically request ECG data to complete its review.

Lastly, it should be pointed out that with the enactment of the Food and Drug Administration Amendments Act of 2007 (FDAAA), Section 505(o) of the Federal Food, Drug, and Cosmetic Act states that FDA can require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes if FDA makes certain findings required by the statute (section 505(o)(3)(A)). To my knowledge, FDA has not made such a finding with respect to Aldara since FDAAA went into effect on March 25, 2008.

B. Systemic exposures to imiquimod and concerns regarding cardiac repolarization

Zyclara at maximal use conditions (i.e., 2 packets or 18.75 mg daily over the full face and scalp for 3 weeks, as evaluated in study GW01-0706) results in mean peak serum imiquimod levels of 0.323 ± 0.159 ng/mL at day 21; the highest concentration observed was 0.588 ng/mL. Graceway believes that the risk of a clinically meaningful QT effect with these low exposures is non-existent. For imiquimod to exhibit a QT prolonging effect at these concentrations it would need to be an extremely potent proarrhythmic drug.

In a consult dated September 15, 2009, the DCRP QT/IRT stated that "A key question is whether the new formulation will lead to an increase in systemic exposure compared to the old formulation... If the new formulation will lead to the potential of higher systemic exposures..." a case could be made for additional testing, such as a thorough QT study. In recent discussions held to address this appeal, the DCRP QT/IRT clarified that, in their experience, no product with exposures this low has been associated with effects on cardiac repolarization. This experience, taken together with the apparent lack of effect on cardiac repolarization in analyses of ECG data submitted from oral imiquimod exposure in the Type A meeting package, lead the DCRP QT/IRT to conclude that imiquimod cream offers minimal risk to delay cardiac repolarization. Further, the DCRP QT/IRT does not recommend that a thorough QT study be conducted, although some amount of ECG monitoring in the clinical development program would have been desirable. DDDP acknowledges this revised recommendation. Further internal discussion regarding the cardiac repolarization risks of small molecules with low systemic exposures is planned, including guidance development regarding appropriate monitoring in clinical trials evaluating such products.

C. Comparative systemic exposures and clinical safety of Zyclara and Aldara

The table below summarizes systemic exposures at steady state following maximal use application of Zyclara or Aldara in AK patients. These regimens exceed recommended dosing with respect to the number of packets applied, frequency or duration of treatment. The results for study 1402-IMI are already labeled.

Graceway notes that a comparison of the Aldara and Zyclara pharmacokinetic profiles in these studies shows that Zyclara falls within peak levels seen with Aldara. In addition, even with the higher exposures in 1520-IMIQ, a study of the application of up to six packets of Aldara 3 times weekly for up to three 16-week cycles in 551 subjects⁶, no new safety concerns, including cardiac safety, were observed.

	C_{max} (ng/mL)		AUC (ng hr/mL)	
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Thus, in accordance with DDDP's advice provided to Graceway at the pre-NDA meeting, these data taken together support the short- and long-term safety of Zyclara.

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F. Conclusions and Recommendations

First, regarding the subject of this formal dispute resolution, that is, the need for a pre-approval thorough QT study, I have considered a) the determinations by FDA (in 1997 and 2004) that the benefits of Aldara treatment outweigh its risks, b) the determination (in 2005) that labeling of several postmarketing spontaneous adverse events, including cardiovascular events, and continued pharmacovigilance was an acceptable means by which to ensure that the benefits of treatment continued to outweigh the risks, and c) the limited clinical information available

regarding a few highly confounded case reports suggestive of proarrhythmic potential. I have also considered the available pharmacokinetic information for Aldara and Zyclara, and acknowledge both the limitations of cross-study comparisons and the intersubject variability observed in pharmacokinetic assessments. I have also considered the adverse event profiles for Aldara as labeled and with maximal use, and for Zyclara as studied in controlled clinical trials, again acknowledging the limitations of such comparisons. Taken together, I am persuaded that systemic imiquimod exposure with maximal use of Zyclara is sufficiently bracketed by the imiquimod exposures seen with maximal use of Aldara, and that these exposures are sufficiently low to provide reassurance that topical imiquimod offers minimal risk with regard to cardiac repolarization. In addition, Zyclara is intended for a patient population with AK that is analogous to that for Aldara, not a population at greater potential risk for cardiovascular adverse events. Therefore, I conclude that, with regard to NDA 022483, a thorough QT study is not needed pre-approval.

Second, recent discussions involving DDDP and consulting groups have taken place to consider a path forward for NDA 022483 and what further study might be warranted post-approval. The DCRP QT/IRT has reviewed the ECG data from R-837-009 submitted in the post-action meeting package, and considering the subnanomolar systemic exposure with topical imiquimod, is sufficiently reassured that a thorough QT study is not needed. Further, the DCRP QT/IRT has advised that a thorough QT study is not an efficient means to assess symptomatic tachyarrhythmias, such as SVT. Existing data may address the potential for imiquimod to trigger symptomatic tachyarrhythmias and should be submitted for review as described below.

Graceway should, therefore, submit a complete response to its October 16, 2009 complete response letter to include the following:

- proposed product labeling;
- a safety update that includes:
 - the full study report for R-837-009, including ECG tracings; and
 - information to address the possibility that imiquimod may trigger symptomatic tachyarrhythmias, such as SVT. This information should include a) a review of the clinical trial safety database for an imbalance of adverse events such as syncope, palpitations and dizziness for imiquimod compared to placebo, and b) an assessment of available data on heart rate (e.g., change from baseline and outlier analysis by dose/concentration); and
- a draft protocol synopsis for a postmarketing controlled clinical trial designed to assess the affects of topical imiquimod on heart rhythm.

This submission will be considered a Class 1 resubmission and be reviewed on a two-month clock.

{See appended electronic signature page}

Julie Beitz, MD
Director, Office of Drug Evaluation III
Office of New Drugs

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/

JULIE G BEITZ
01/15/2010



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: January 7, 2010

From: Suchitra Balakrishnan, M.D., Ph.D.
Shari Targum, M.D.
Christine Garnett, Pharm.D.
Division of Cardiovascular and Renal Products, CDER

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

To: Julie Beitz, M.D.
Director, ODE-3

Subject: Formal Dispute Resolution for NDA 22-483

This memo responds to your December 30, 2009 email regarding the Type A Meeting Package and formal dispute resolution request submitted by Graceway Pharmaceuticals LLC, sponsor of Imiquimod Cream 3.75% under NDA 22-483. We received and reviewed the following materials:

- Type A meeting Package submitted by Graceway dated November 6, 2009
- Formal Dispute resolution request and review materials to FDA submitted by Sponsor dated December 16, 2009
- FDA CR letter for NDA 22-483 dated Oct 16, 2009 and FDA memorandum of meeting minutes dated November 17, 2009
- Previous reviews by the QT-IRT dated May 29, 2009 and DCRP dated September 15, 2009

Overall Comments

In our opinion, based on low systemic exposures and apparent lack of QTc effect from the ECG data submitted to NDA 20-723, a TQT study is *not* needed for imiquimod cream.

Because DDDP is concerned about the possibility of imiquimod to trigger symptomatic SVT, we recommend that the clinical safety database be reviewed for an imbalance of adverse events such as syncope, palpitations and dizziness for imiquimod compared to placebo. The sponsor could

submit previous data evaluating effect on heart rate (e.g., change from baseline and outlier analysis by dose/concentration). In addition, the sponsor could propose a battery of preclinical tests to evaluate the potential for initiating or triggering supraventricular arrhythmias as a post-marketing commitment. A TQT study is not an efficient means to assess the potential of a drug to trigger SVT; our previous review mentioned looking there on the assumption that there was another reason to do the study.

Response to Questions from Dr. Beitz

1. Are the arguments about low systemic exposure sufficient to allay concerns about cardiac repolarization?

Yes. The ICH E14 guidelines apply to new drugs with systemic bioavailability. At therapeutic and suprathreshold doses of imiquimod cream, plasma concentrations are in the low nanomolar range. The highest concentration obtained following daily administration of 2 packets of 3.75% cream for three weeks (study GW01-0706) was 0.6 ng/ml (corresponds to 0.24 nM of free imiquimod). Potent inhibitors of the hERG channel have IC₅₀ values in the low nM range. For example, the IC₅₀ values for dofetilide and ibutilide are in the range of 15 to 30 nM. Therefore, the low systemic bioavailability of imiquimod alone gives reassurance that imiquimod has minimal risk to delay cardiac repolarization. This is also confirmed by the results of routine ECG monitoring for Aldara (NDA 20-723) and by the ECGs obtained following oral imiquimod administration — as described in our response to question 2.

A similar rationale led to waiving TQT studies for other drugs with low systemic bioavailability, such as with (b)(4), Botox (BB IND 8142) (b)(4), (b)(4) (b)(4), (b)(4) and (b)(4). For drugs with low systemic bioavailability, the QT-IRT recommends obtaining routine safety ECGs in the clinical studies.

2. Do we need to (re-) review the ECG data from oral exposures formally or not?

We reviewed eRT's analysis of QTc data obtained from Study R-837-009. Based on our review, 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 and there was no significant exposure-response relationship for imiquimod or its metabolite. There was also no dose-response in the mean change from baseline QTcF data.

In this study, 27 subjects (90% of the total receiving active drug) achieved C_{max} > 100 ng/mL (more than 100-fold greater than the mean C_{max} observed in Study GW01-0706 subjects at maximum exposure to the 3.75% preparation).

We do not think a formal review of ECG waveforms is necessary.

3. If we need further study, is a thorough QT study with Holter monitoring the study we really need?

No. The concern appears to be related to episodes of supraventricular tachycardia (SVT), which is unrelated to effects on the QT interval. A thorough QT study with Holter monitoring could

show effects on QT interval or arrhythmias, with suprathreshold doses of drug. Routine Holter monitoring might reveal asymptomatic atrial arrhythmias of uncertain clinical consequence. Furthermore, there might be a large degree of variability in the extent of atrial ectopy/asymptomatic arrhythmias. If one chose the route of Holter monitoring for arrhythmias, one would need to define, in advance, what constitutes a clinically meaningful signal.

If one is concerned about symptomatic SVT, then one should review the safety database for adverse events such as syncope, palpitations and dizziness. In addition, preclinical data would be helpful. From a mechanistic standpoint, drugs that have been known to “trigger” re-entry SVT include stimulants (e.g., caffeine, thyrotoxicosis, cocaine, beta-agonists), tobacco and alcohol. Does imiquimod have stimulant activity in the therapeutic range? SVT can be also triggered by nonpharmacologic events (e.g., anxiety, infection, myocarditis).¹ Digitalis has been associated with increased atrial automaticity and one can look for digitalis-like electrophysiologic effects.

It might be more informative, therefore, to look at available data, or have the sponsor submit previous data evaluating effect on heart rate (e.g., change from baseline and outlier analysis by dose/concentration). Also helpful would be a review of the safety database, with data mining, for adverse events suggestive of arrhythmias. In addition, the sponsor could propose a battery of preclinical tests to evaluate the potential for initiating or triggering supraventricular arrhythmias.

4. We know that topical imiquimod induces systemic levels of IFN alfa, and that IFN alfa therapy can induce fever, chills, malaise, tachycardia, myalgias and rigors. Would a study that evaluated the relationship of imiquimod-induced IFN levels and heart rate be useful? If so, what would this study look like?

The sponsor has submitted individual patient HR values from Study R-837-009. Following single oral doses of 100 mg, 200 mg, 250 mg and 300 mg imiquimod, which give >100-fold greater imiquimod exposures than with imiquimod cream 3.75%, most HR values are around 70 bpm or less which is reassuring.

BACKGROUND

Imiquimod (Zyclara) 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 daily dosing vs. twice weekly dosing for Aldara.

DDDP took a CR action on the Zyclara NDA 22-483 (imiquimod cream, 3.75%) on Oct 16, 2009 stating the following deficiencies.

“1. Electrocardiographic studies were not conducted during the development of your product and the effect of imiquimod on cardiac repolarization and arrhythmias is

¹ Source: ACP: Pier, under Supraventricular Tachycardia.

unknown. The comparative bioavailability of Zyclara and Aldara (used as labeled) is unknown.

In the absence of adequate information about the comparative bioavailability of Zyclara relative to Aldara and adequate data demonstrating that Zyclara does not affect cardiac repolarization, the potential risks of Zyclara are not justified by the potential benefits to patients with actinic keratoses of the face or scalp.

Information Needed for Resolution

Conduct of a thorough QT study with Holter monitoring to demonstrate the impact of your product on cardiac repolarization and heart rate.”

There was a post-action meeting held with the sponsor on Nov 17, 2009 in which the sponsor pointed to several studies with oral or topical imiquimod that included ECG monitoring (see below). These studies were submitted to the original Aldara NDA (imiquimod cream, 5%) but the sponsor did not reference these data in the Zyclara NDA. At the post-action meeting, DDDP indicated that these studies were not relevant as they were not formal TQT studies and they still would require a pre-approval TQT study.

The sponsor has now appealed formally to the agency in this regard and has requested involvement of the QT-IRT and Cardiology.

Clinical ECG Data from NDA 20-723

Upon receipt of the Complete Response letter, Graceway reviewed previous pharmacokinetic and efficacy studies conducted by 3M, the original sponsor for Aldara, and determined that electrocardiograms (ECGs) were included as part of at least 7 clinical studies. The following table describes clinical studies of imiquimod with ECG recordings submitted in NDA 20-723.

Submission	Study No./ Title	No. Subjects	Dose groups (n)	Pharmacokinetics	ECG Procedures	Relevant ECG Findings
Topical studies						
EGW NDA Date 25 JUL 1996 Vol. 2.34 Page 212	R-837T-003-01 One-percent R-837 Cream Topical Safety Trial	30 males	1% Cream 5mg (10) 10mg (10) 15mg (10) Once daily for 7 days on forearm	R-837 mean C _{max} < 1 ng/mL* (in 28 subj) 1.5 ng/mL (1 subject) 2.1 ng/mL (1 subject) S-26704 mean C _{max} < 1 ng/mL* (2 subjects) *lower limit of detection	12-lead ECG pre-study and on days 3, 7 and at least 24 hours post-study. Atrial/ventricular rates and PR, QRS and QT uncorrected were obtained, QT corrected and JT (QT-QRS) intervals were determined and compared to baseline.	No clinically significant findings in heart rates and ECG intervals, vital signs, or laboratory results that could be attributed to the effect of R-837. The QT, QT corrected, and JT intervals tended to decrease compared with baseline for all dose groups. Some of these changes were statistically significant, especially for the 15-mg group.
EGW NDA Date 25 JUL 1996 Vol. 2.138 Page 6	R-837T-004-01 Efficacy Trial Evaluation R-837T Cream for the Treatment of Genital/Perianal Warts Following Intermittent Application	40 males	1% Cream (18) 5% Cream (22) applied to genital warts Three times weekly for 3 weeks. Varying permissible amounts of total cream applied	None measured	12-lead ECG Assessed pre- study and 3-8 hours after last dose removed.	No clinically significant changes in ECGs from pre- study for any patient.
EGW NDA Date 25 JUL 1996 Vol. 2.139 Page 1	R-837T-005 Efficacy Trial Evaluation R-837T Cream for the Treatment of Genital/Perianal Warts Following a Ten-Day Daily Application	49 males	1% Cream (22) 5% Cream (27) Once daily for 10 days. Warts treated with cream volume up to 50mg for all days determined by volume to treat warts on day 1	None measured	12-lead ECG assessed pre- study and 3-8 hours after last dose removed	There were no clinically significant changes in ECGs for any patient. The only significant change from post study was a significant increase from prestudy for the QRS interval.

Submission	Study No./ Title	No. Subjects	Dose groups (n)	Pharmacokinetics	ECG Procedures	Relevant ECG Findings
EGW NDA Date 25 JUL 1996 Vol. 2.35 Page 1 Vol. 2.42 p. 2	R-837T-008-01 Five-percent R-837T Topical Safety Trial	30 males	Once daily for 7 days applied to forearm 5 mg (6) 10 mg (6) 15 mg (6) 20 mg (6) 25 mg (6)	R-837 measured at regular intervals, none detected	Baseline, treatment phase and post study evaluations with 12- lead ECG with interpretation	Two subjects (#6, 5mg and #20, 20 mg) experienced unifocal PVCs without clinical significance. Subject (#6) experienced irregular pulse on days 5 and 7. Subject 20 was discontinued from study day 3 because of PVCs on ECG. There were a few occurrences of statistically significant changes in ECG intervals during the study, but no trends over time or dose levels were observed.
Oral studies						
EGW NDA Date 25 JUL 1996 Vol. 2.38 Page 1	R-837-009 Rising Dose Safety and Pharmacokinetic Study of Oral R-837 in Healthy Volunteers	40 males	Single oral dose, escalating cohort Placebo (10) 100 mg (6) 200 mg (6) 250 mg (6) 300 mg (12)	Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hrs post dose R-837 mean C _{max} 100mg: 120 ng/mL 200mg: 281 ng/mL 250mg: 359 ng/mL 300 mg: 528 ng/mL S-26704 mean C _{max} 100mg: 14.7 ng/mL 200mg: 24.7 ng/mL 250mg: 25.4 ng/mL 300 mg: 40.1 ng/mL	ECG within 2 weeks of study, pre-dose, 2, 4, 8, 24, and 48 hours after dose	Safety summary indicated no clinically significant changes in ECGs for any subject during trial. Analysis of QT intervals displayed in Table 7 of CSR.

Submission	Study No./ Title	No. Subjects	Dose groups (n)	Pharmacokinetics	ECG Procedures	Relevant ECG Findings
EGW NDA Date 25 JUL 1996 Vol. 2.36 Page 121	R-837-018 A Single-dose Relative Bioavailability Study Comparing Oral Imiquimod (R-837) Administered in a Fasted State with Administration in a Nonfasted State and a Subcutaneous Imiquimod Reference	20 males enrolled, 16 completed	30mg subcutaneous 100mg fasting 100mg non-fasting crossover	R-837 <u>mean C_{max}</u> subQ: 123 ng/mL fasting: 128 ng/mL nonfasting: 120 ng/mL	Atrial and ventricular rates and ECG intervals of PR, QRS, and QT uncorrected were obtained from ECGs performed prestudy and after the 24 hr blood collection in the last treatment period. QT corrected and JT (QT-QRS) intervals were calculated	No clinically significant or statistically significant differences were seen between the prestudy and poststudy mean atrial and ventricular rates. While the mean PR interval measured 24 hr following the last treatment for study completers was statistically significantly greater than the prestudy mean value, this finding was not deemed clinically significant. There were no other statistically significant changes in ECG intervals.
EGW NDA Date 25 JUL 1996 Vol. 2.263 Page 1	R-837-019 Relationship of Circulating Interferon to Immunomodulating Action of Imiquimod (R-837) in Healthy Volunteers	24 males	Single oral dose Placebo (6) 100mg (6) 200mg (6) 300mg (6)	Predose, 1, 2, 3, 4, 6, 8, 12 and 24 hrs post dose R-837 <u>mean C_{max}</u> 100mg: 126 ng/mL 200mg: 272 ng/mL 300 mg: 424 ng/mL S-26704 <u>mean C_{max}</u> 100mg: 17 ng/mL 200mg: 30 ng/mL 300 mg: 34 ng/mL S-27700 <u>mean C_{max}</u> 100mg: 24 ng/mL 200mg: 44 ng/mL 300 mg: 38 ng/mL	Atrial and ventricular rates and PR, QRS, and QT uncorrected intervals were obtained from 12-lead ECGs performed prestudy and 24 hours following dose administration. Rhythm strips (of at least 10 complexes recorded at 25 mm/sec) were also performed at 2, 4, and 8 hours after dosing to obtain additional measures of PR, QRS, and QT uncorrected intervals. QT corrected and JT (QT-QRS) intervals were calculated. Changes from baseline values for these parameters were compared separately for each dose using paired t-test and Wilcoxon Signed Rank Tests.	Mean uncorrected QT intervals were decreased compared to baseline at each observed time point for all four dose groups. These mean changes were as large in the placebo group as in the imiquimod treated groups. While the changes were statistically significant at most time points, they were not clinically significant. Corrected QT values were calculated for 0 and 24 hours only, because ventricular rates were not measured at 2, 4, and 8 hours postdose. A statistically significant decrease in mean QT corrected interval at 24 hours post dosing was observed for the placebo subjects.

Abnormal ECGs were reported for four of the clinical program participants exposed to imiquimod. Three of these participants were healthy subjects enrolled in phase I safety trials (R-837T-03 and R-837T-008); and one participant was a patient with genital warts enrolled in a phase III efficacy trial (1004-IMIQ).

Table 8.5.A Summary of Participants With Abnormal ECG Reports

Trial-site	Participant Number	Age/Gender	Treatment Group	Maximum Exposure	ECG Report
R-837T-003	021	47 years/Male	1% IMIQ	105 mg	Day 7 and post trial ECGs abnormal. Sinus tachycardia consistent with elevate pulse associated with temperature elevation. ECG changes not clinically significant.
R-837T-008	006	29 years/Male	5% IMIQ	35 mg	Day 5, day 7, and post trial ECGs reported as abnormal due to frequent or occasional PVCs. Follow-up ECG was normal. Subject also experienced episodes of irregular pulse which were judged to be unlikely due to imiquimod application.
R-837T-008	020	63 years/Male	5% IMIQ	60 mg	Subject discontinued on day 3 due to abnormal ECG results. Five days post trial discontinuation, the ECG results were still abnormal. The subject was asymptomatic and referred to his personal physician. The abnormal ECG reports were judged to be unlikely to be due to imiquimod application.
1004-IMI-Q-03	004	64 years/Male	5% IMIQ	230.4 mg	Patient found to have irregular rhythm at post trial exam. Patient subsequently hospitalized and converted to normal sinus rhythm. Five days post treatment patient asymptomatic, resolved irregularity. The irregular rhythm was not attributed to imiquimod application.

Source: ISS NDA 20-723

Overall, the sponsor reported that there were no clinically significant imiquimod-related changes in ECGs observed during the clinical program. Except for Study R-837-009 (discussed below), ECG evaluations were not rigorous (typically pre-dose and single post-dose ECG).

Study R-837-009 ECG Findings

R-837-009 is an oral dose escalation study that was performed in 1989 in healthy subjects. 12-lead ECGs were performed prior to the treatment day and at hours 0, 2, 4, 8, 24 and 48 hours on the day of treatment, and PK samples were drawn at all ECG time points. All ECGs were recorded with the same model of electrocardiograph, and the QT intervals were measured by hand on the original paper recordings. Imiquimod was administered orally at 4 escalating doses: 100 mg, 200 mg, 250 mg and 300 mg. In the first three dose groups, 6 subjects received imiquimod and 2 received placebo. Twelve subjects received 300 mg and 4 received placebo in the last dose group. C_{max} ranged from 67 to 229 ng/mL in the 100 mg group and from 314 -800 ng/mL in the 300 mg group. In total, 27 subjects (90% of the total receiving active drug) achieved C_{max} > 100 ng/mL (more than 100-fold greater than the mean C_{max} observed in Study GWOI-0706 subjects at maximum exposure to the 3.75% preparation).

For the re-analysis, the sponsor reports that ECG QT interval and ventricular hear 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 S 26704 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 and presented in Appendix 3. 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	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)

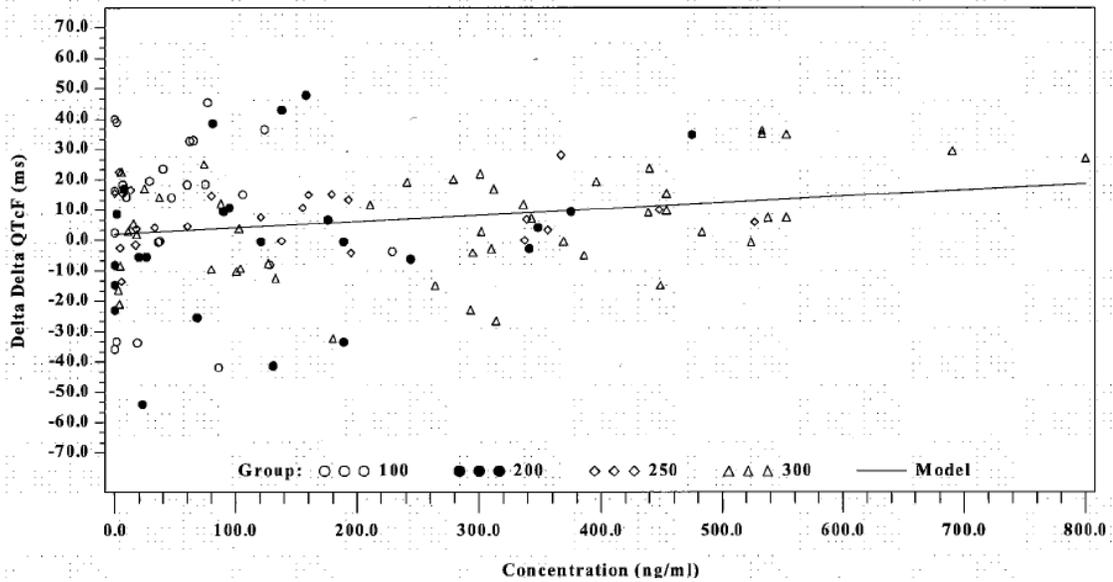
Parameter Timepoint Category	100 (N=6)	200 (N=6)	250 (N=6)	300 (N=12)	Placebo (N=10)
Change from Baseline in QTcF (msec)					
Day 1 Hour 2					
≤ 30 msec	4 (66.7)	4 (66.7)	6 (100.0)	12 (100.0)	9 (90.0)
> 30 - ≤ 60 msec	2 (33.3)	2 (33.3)	0	0	1 (10.0)
> 60 msec	0	0	0	0	0
Change from Baseline in QTcF (msec)					
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 Comment: No subject experienced an absolute QTcF over 450 ms at doses at exposures over 100-fold compared to the topical preparation.

A PK-PD analysis based on plasma imiquimod concentrations and $\Delta\Delta\text{QTcF}$ in each subject showed a shallow slope of 0.024 ms per ng/mL which is not statistically significant (p-value = 0.12) using linear mixed effect model (see Sponsor's Figure 4). Similar findings were reported when metabolite concentrations were used as the independent variable in the mixed model.

Figure 4 Study R-837-009 Imiquimod Concentration-Response Modeling - Delta Delta QTcF



Adverse Events of Concern raised by the Review Division

The review division has raised concern regarding the following Case Reports:

ISR 4991080, US (2005): A 44 year old man using 5% imiquimod cream three times a week to treat BCC on his forehead was taken to the emergency room twice for supraventricular arrhythmia events. In both instances the events occurred approximately 15 hours after removal of imiquimod cream. He reported experiencing palpitations, increased blood pressure, and a supraventricular tachycardia (SVT) of 150 beats per minute. There were no reports of syncope or pre-syncope.

AERS #3348851; 1999; US: A 34 year old woman applied two doses of 5% imiquimod cream to treat EGW and reported that both times she experienced tachycardia 10 minutes after application, which lasted 30 minutes. She left the cream on for 8 hours before washing it off. She did not report syncope or presyncope, nor did she have an ECG.

AERS #3506425; 2000; US: A 14 year old boy with a history of heart murmur and valvular insufficiency used 5% imiquimod cream daily for common warts on his arms and hands. After using Aldara for 13 days he experienced an irregular and rapid heart rate, which abated when he stopped using imiquimod and returned when he restarted imiquimod treatment. He did not have an ECG, nor reported syncope or pre-syncope.

AERS #4191114; 2004; US: A 71 year old man using 5% imiquimod cream on his nose to treat BCC applied it three times weekly. After about two months, the man was found dead. No autopsy was performed. The cause of the man's death is unknown due to the limited information received in the case. It is therefore unknown whether he had a cardiac repolarization event

Subject 01/210 in Study GW01-0702: A 65 year old woman in a Zyclara clinical trial completed her treatment using 2.5% imiquimod cream on April 2, 2008. She was seen weekly and reported no cardiac symptoms during the treatment phase. Her medical history included hypertension and arrhythmias since 2004. 86 On May 17, 2008 - 45 days after discontinuing imiquimod treatment - she experienced palpitations and syncope while driving, and reported them to her primary care physician on May 28. An ECG demonstrated PVCs every 30 seconds and the patient was referred to a cardiologist, who was reported to have performed an outpatient cardiac ablation procedure and to have prescribed medication and external heart monitoring. The cardiologist's electrophysiologic study reported that she had easily inducible atrial fibrillation with normal AV nodal conduction, but no inducible ventricular tachycardia or ventricular fibrillation.

Reviewer's Comments:

- *ISR 4991080, US (2005): Association between imiquimod and symptomatic supraventricular arrhythmias can probably be best examined by review of the clinical trial database and non-clinical testing. See response to Question No 3 regarding supraventricular arrhythmias.*
- *AERS #3348851, AERS #3506425 and AERS #4191114: Insufficient information is available in this case to determine association to study drug or type of arrhythmia.*
- *Subject 01/210 in Study GW01-0702: The event occurred 45 days after discontinuing the drug.*

MGPS Data mining analyses for Cardiac AEs with Imiquimod

An MGPS data mining analyses of AERS for all MedDRA PT's related to arrhythmias (including conduction defects), congestive heart failure, coronary artery disease and AEs related to QT prolongation was conducted with mean signal score (EBGM value) set at zero. The EBGM values for events of concern (supraventricular arrhythmias and QT related events) were all below one, indicating incidence similar to background rate. It is interesting to note that most events also had EB-95 values less than two.

Configuration: CBAERS BestRep (S) (v2) **Run :** Generic (S) **Run ID:** 1940

Dimension: 2 **Selection Criteria:** Generic name(Imiquimod) + PT(...)

28 rows Sorted by Generic name, EBGm desc

Generic name	PT	HLT	SOC	N	EBGM	EB05	EB95
Imiquimod	Atrial septal defect	Cardiac septal defects congenital	Cong	2	1.61	0.526	4.04
Imiquimod	Ventricular septal defect acquired	Myocardial disorders NEC	Card	1	1.19	0.278	3.69
Imiquimod	Presyncope	Neurological signs and symptoms NEC	Nerv	1	1.07	0.252	3.33
Imiquimod	Heart disease congenital	Cardiac disorders congenital NEC	Cong	1	1.05	0.247	3.26
Imiquimod	Acute coronary syndrome	Ischaemic coronary artery disorders	Card	1	0.995	0.233	3.08
Imiquimod	Supraventricular tachycardia	Supraventricular arrhythmias	Card	2	0.817	0.266	2.04
Imiquimod	Arteriosclerosis coronary artery	Coronary artery disorders NEC	Card	1	0.720	0.169	2.23
Imiquimod	Sudden death	Death and sudden death	Genrl	2	0.539	0.176	1.34
Imiquimod	Cardiac failure	Heart failures NEC	Card	4	0.527	0.230	1.07
Imiquimod	Oedema peripheral	Oedema NEC	Genrl	12	0.423	0.260	0.657
Imiquimod	Pulmonary congestion	Pulmonary oedemas	Resp	1	0.392	0.092	1.21
Imiquimod	Dizziness	Neurological signs and symptoms NEC	Nerv	26	0.386	0.277	0.525
Imiquimod	Haemoptysis	Coughing and associated symptoms	Resp	1	0.381	0.089	1.18
Imiquimod	Cardiomyopathy	Cardiomyopathies	Card	1	0.347	0.081	1.08
Imiquimod	Atrial fibrillation	Supraventricular arrhythmias	Card	2	0.305	0.100	0.762
Imiquimod	Angina pectoris	Ischaemic coronary artery disorders	Card	1	0.280	0.066	0.868
Imiquimod	Palpitations	Cardiac signs and symptoms NEC	Card	5	0.255	0.121	0.486
Imiquimod	Chest discomfort	Pain and discomfort NEC	Genrl	2	0.253	0.082	0.630
Imiquimod	Chest pain	Pain and discomfort NEC	Genrl	10	0.246	0.145	0.398
Imiquimod	Syncope	Disturbances in consciousness NEC	Nerv	4	0.232	0.102	0.470
Imiquimod	Dyspnoea	Breathing abnormalities	Resp	15	0.225	0.146	0.336
Imiquimod	Tachycardia	Rate and rhythm disorders NEC	Card	5	0.212	0.101	0.404
Imiquimod	Cardiac failure congestive	Heart failures NEC	Card	1	0.167	0.039	0.519
Imiquimod	Arrhythmia	Rate and rhythm disorders NEC	Card	1	0.161	0.038	0.499
Imiquimod	Pulmonary oedema	Pulmonary oedemas	Resp	1	0.158	0.037	0.490
Imiquimod	Myocardial infarction	Ischaemic coronary artery disorders	Card	3	0.150	0.058	0.331
Imiquimod	Cardiac disorder	Cardiac disorders NEC	Card	1	0.149	0.035	0.462

Generic name	PT	HLT	SOC	N	EBGM	EB05	EB95
Imiquimod	Cardiac arrest	Ventricular arrhythmias and cardiac arrest	Card	1	0.108	0.025	0.334
ID:	1940						
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) (v2)						
Configuration Description:	CBAERS data; best representative cases; suspect drugs only; with duplicate removal						
As Of Date:	12/17/2009 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:	12/26/2009 22:03:32 EST						
User:	Suchitra Balakrishnan						
Source Database:	Source Data: CBAERS data from Extract provided by CBER as of 12/17/2009 00:00:00 loaded on 2009-12-24 04:29:45.0						

Dimension: 2 Selection Criteria: Generic name(Imiquimod) + PT(Accelerated idioventricular rhythm, Accessory cardiac pathway, Acquired cardiac septal defect, Acute coronary syndrome, Acute endocarditis, Acute left ventricular failure, Acute myocardial infarction, Acute pulmonary oedema, Acute right ventricular failure, Adams-Stokes syndrome, Agonal rhythm, Anaesthetic complication cardiac, Angina pectoris, Angina unstable, Anomalous atrioventricular excitation, Arrhythmia, Arrhythmia neonatal, Arrhythmia supraventricular, Arrhythmogenic right ventricular dysplasia, Arteriosclerosis coronary artery, Arteriospasm coronary, Arteritis coronary, Ascites, Athletic heart syndrome, Atrial conduction time prolongation, Atrial fibrillation, Atrial flutter, Atrial hypertrophy, Atrial rupture, Atrial septal defect, Atrial septal defect acquired, Atrial tachycardia, Atrial thrombosis, Atrioventricular block, Atrioventricular block complete, Atrioventricular block first degree, Atrioventricular block second degree, Atrioventricular conduction time shortened, Atrioventricular dissociation, Atrioventricular extrasystoles, Atrioventricular septal defect, Atypical mycobacterium pericarditis, Autoimmune myocarditis, Bacterial pericarditis, Benign pericardium neoplasm, 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 amyloidosis, Cardiac aneurysm, Cardiac arrest, Cardiac arrest neonatal, Cardiac asthma, Cardiac autonomic neuropathy, Cardiac cirrhosis, Cardiac death, Cardiac discomfort, Cardiac disorder, Cardiac failure, Cardiac failure acute, Cardiac failure chronic,

Cardiac failure congestive, Cardiac failure high output, Cardiac fibrillation, Cardiac flutter, Cardiac function disturbance postoperative, Cardiac granuloma, Cardiac hypertrophy, Cardiac infection, Cardiac perforation, Cardiac procedure complication, Cardiac pseudoaneurysm, Cardiac sarcoidosis, Cardiac septal defect, Cardiac septal defect residual shunt, Cardiac siderosis, Cardiac tamponade, Cardiac vein dissection, Cardiac vein perforation, Cardiac ventricular disorder, Cardio-respiratory arrest, Cardio-respiratory arrest neonatal, Cardio-respiratory distress, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, Cardiomyopathy acute, Cardiomyopathy alcoholic, Cardiomyopathy neonatal, Cardiopulmonary failure, Cardioresenal syndrome, Cardiotoxicity, Cardiovascular deconditioning, Cardiovascular disorder, Cardiovascular insufficiency, Cardiovascular syphilis, Carditis, Chest discomfort, Chest pain, Chordae tendinae rupture, Chronic left ventricular failure, Chronic right ventricular failure, Chronotropic incompetence, Clubbing, Complications of transplanted heart, Conduction disorder, Congestive cardiomyopathy, Cor pulmonale, Cor pulmonale acute, Cor pulmonale chronic, Coronary artery aneurysm, Coronary artery dilatation, Coronary artery disease, Coronary artery dissection, Coronary artery embolism, Coronary artery insufficiency, Coronary artery occlusion, Coronary artery perforation, Coronary artery reocclusion, Coronary artery restenosis, Coronary artery stenosis, Coronary artery thrombosis, Coronary bypass thrombosis, Coronary no-reflow phenomenon, Coronary ostial stenosis, Coxsackie carditis, Coxsackie endocarditis, Coxsackie myocarditis, Coxsackie pericarditis, Cyanosis, Cyanosis central, Cytomegalovirus myocarditis, Cytomegalovirus pericarditis, Cytotoxic cardiomyopathy, Diabetic cardiomyopathy, Diastolic dysfunction, Dilatation atrial, Dilatation ventricular, Dissecting coronary artery aneurysm, Dizziness, Dizziness exertional, Dizziness postural, Dressler's syndrome, Dyspnoea, Dyspnoea at rest, Dyspnoea exertional, Dyspnoea paroxysmal nocturnal, Electromechanical dissociation, Endocardial disease, Endocardial fibroelastosis, Endocardial fibrosis, Endocarditis, Endocarditis Q fever, Endocarditis bacterial, Endocarditis candida, Endocarditis enterococcal, Endocarditis fibroplastica, Endocarditis gonococcal, Endocarditis haemophilus, Endocarditis helminthic, Endocarditis histoplasma, Endocarditis meningococcal, Endocarditis noninfective, Endocarditis pseudomonas, Endocarditis rheumatic, Endocarditis staphylococcal, Endocarditis syphilitic, Endocarditis viral, Eosinophilic myocarditis, Extrasystoles, Fluid overload, Foetal arrhythmia, Foetal cardiac disorder, Foetal heart rate deceleration, Foetal heart rate disorder, Fungal endocarditis, Gastrocardiac syndrome, Glycogen storage disease type II, Gravitational oedema, Grey syndrome neonatal, HIV cardiomyopathy, Haemoptysis, Haemorrhage coronary artery, Heart alternation, Heart block congenital, Heart disease congenital, Heart injury, Heart transplant rejection, Heart-lung transplant rejection, Hepatic congestion, Hepatojugular reflux, Holt-Oram syndrome, Hyperdynamic left ventricle, Hyperkinetic heart syndrome, Hypertensive cardiomegaly, Hypertensive cardiomyopathy, Hypertensive heart disease, Hypertrophic cardiomyopathy, In-stent coronary artery restenosis, Interventricular septum rupture, Intracardiac mass, Intracardiac thrombus, Intrapericardial thrombosis, Ischaemic cardiomyopathy, Jugular vein distension, Kearns-Sayre syndrome, Kounis syndrome, Kyphoscoliotic heart disease, Laryngeal dyspnoea, Left atrial dilatation, Left atrial hypertrophy, Left ventricular dysfunction, Left ventricular failure, Left ventricular hypertrophy, Lipomatous hypertrophy of the interatrial septum, Localised oedema, Long QT syndrome, Long QT syndrome congenital, Low cardiac output syndrome, Lown-Ganong-Levine syndrome, Lupus endocarditis, Lupus myocarditis, Malarial myocarditis, Malignant hypertensive heart disease, Malignant pericardial neoplasm, Meningococcal carditis, Microvascular angina, Myocardial abscess, Myocardial calcification, Myocardial depression, Myocardial fibrosis, Myocardial haemorrhage, Myocardial infarction, Myocardial ischaemia, Myocardial oedema, Myocardial reperfusion injury, Myocardial rupture, Myocarditis, Myocarditis bacterial, Myocarditis helminthic, Myocarditis infectious, Myocarditis meningococcal, Myocarditis mycotic, Myocarditis post infection, Myocarditis septic, Myocarditis syphilitic, Myocarditis toxoplasmal, Myoglobinuria, Myoglobinuria, Myopericarditis, Negative cardiac inotropic effect, Neonatal cardiac failure, Neonatal tachycardia, Nocturnal dyspnoea, Nodal arrhythmia, Nodal rhythm, Non-obstructive cardiomyopathy, Oedema due to cardiac disease, Oedema peripheral, Orthopnoea, Orthostatic intolerance, Ortner's syndrome, Osler's nodes, Pacemaker complication, Pacemaker generated arrhythmia, Palpitations, Papillary muscle disorder, Papillary muscle haemorrhage, Papillary muscle infarction, Papillary muscle rupture, Parasystole, Paroxysmal arrhythmia, Pericardial calcification, Pericardial disease, Pericardial effusion, Pericardial effusion malignant, Pericardial fibrosis, Pericardial haemorrhage, Pericardial neoplasm, Pericardial rub, Pericarditis, Pericarditis adhesive, Pericarditis amoebic, Pericarditis constrictive, Pericarditis fungal, Pericarditis gonococcal, Pericarditis helminthic, Pericarditis histoplasma, Pericarditis infective, Pericarditis lupus, Pericarditis malignant, Pericarditis meningococcal, Pericarditis mycoplasmal, Pericarditis rheumatic, Pericarditis syphilitic, Pericarditis tuberculous, Pericarditis uraemic, Peripartum cardiomyopathy, Peripheral oedema neonatal, Platypnoea, Pleuropericarditis, Pneumopericardium, Positive cardiac inotropic effect, Post procedural myocardial infarction, Postinfarction angina, Postpericardiotomy syndrome, Postural orthostatic tachycardia syndrome, Presyncope, Prinzmetal angina, Propofol infusion syndrome, Pulmonary artery wall hypertrophy, Pulmonary congestion, Pulmonary oedema, Pulmonary oedema neonatal, Purulent pericarditis, Radiation pericarditis, Rebound tachycardia, Reperfusion arrhythmia, Restrictive cardiomyopathy, Rhabdomyoma, Rheumatic fever, Rheumatic heart disease, Rhythm idioventricular, Right atrial dilatation, Right atrial hypertrophy, Right ventricular dysfunction, Right ventricular failure, Right ventricular hypertrophy, Shoshin beriberi, Sick sinus syndrome, Silent myocardial infarction, Sinoatrial block, Sinus arrest, Sinus arrhythmia, Sinus bradycardia, Sinus tachycardia, Somatoform disorder cardiovascular, Splinter haemorrhages, Stress cardiomyopathy, Subacute endocarditis, Subclavian coronary steal syndrome, Subendocardial ischaemia, Sudden cardiac death, Sudden death, Supraventricular extrasystoles, Supraventricular tachyarrhythmia, Supraventricular tachycardia, Syncope, Syphilitic endocarditis of heart valve, Tachyarrhythmia, Tachycardia, Tachycardia foetal, Tachycardia paroxysmal, Torsade de pointes, Transfusion-related circulatory overload, Trifascicular block, Univentricular heart, Ventricle rupture, Ventricular arrhythmia, Ventricular asystole, Ventricular dysfunction, Ventricular dyskinesia, Ventricular extrasystoles, Ventricular failure, Ventricular fibrillation, Ventricular flutter, Ventricular hyperkinesia, Ventricular hypertrophy, Ventricular hypokinesia, Ventricular pre-excitation, Ventricular remodeling, Ventricular septal defect, Ventricular septal defect acquired, Ventricular tachyarrhythmia, Ventricular tachycardia, Viral cardiomyopathy, Viral myocarditis, Viral pericarditis, Wandering pacemaker, Withdrawal arrhythmia, Wolff-Parkinson-White syndrome,

SELECT * FROM OutputData_1940 WHERE (DIM=2 AND ((P1='D' AND ITEM1 IN ('Imiquimod') AND P2='E' AND ITEM2 IN ('Accelerated idioventricular rhythm','Accessory cardiac pathway','Acquired cardiac septal defect','Acute coronary syndrome','Acute endocarditis','Acute left ventricular failure','Acute myocardial infarction','Acute pulmonary oedema','Acute right ventricular failure','Adams-Stokes syndrome','Agonal rhythm','Anaesthetic complication cardiac','Angina pectoris','Angina unstable','Anomalous atrioventricular excitation','Arrhythmia','Arrhythmia neonatal','Arrhythmia supraventricular','Arrhythmogenic right ventricular dysplasia','Arteriosclerosis coronary artery','Arteriospasm coronary','Arteritis coronary','Ascites','Athletic heart syndrome','Atrial conduction time prolongation','Atrial fibrillation','Atrial flutter','Atrial hypertrophy','Atrial rupture','Atrial septal defect acquired','Atrial tachycardia','Atrial thrombosis','Atrioventricular block','Atrioventricular block complete','Atrioventricular block first degree','Atrioventricular block second degree','Atrioventricular conduction time shortened','Atrioventricular dissociation','Atrioventricular extrasystoles','Atrioventricular septal defect','Atypical mycobacterium pericarditis','Autoimmune myocarditis','Bacterial pericarditis','Benign pericardium neoplasm','Bifascicular block','Bradycardia','Bradycardia foetal','Bradycardia neonatal','Brugada syndrome','Bundle branch block','Bundle branch block bilateral','Bundle branch block left','Bundle branch block right','Cardiac amyloidosis','Cardiac aneurysm','Cardiac arrest','Cardiac arrest neonatal','Cardiac asthma','Cardiac autonomic neuropathy','Cardiac cirrhosis','Cardiac death','Cardiac discomfort','Cardiac disorder','Cardiac failure','Cardiac failure acute','Cardiac failure chronic','Cardiac failure congestive','Cardiac failure high output','Cardiac fibrillation','Cardiac flutter','Cardiac function disturbance postoperative','Cardiac granuloma','Cardiac hypertrophy','Cardiac infection','Cardiac perforation','Cardiac procedure complication','Cardiac pseudoaneurysm','Cardiac sarcooidosis','Cardiac septal defect','Cardiac septal defect residual shunt','Cardiac siderosis','Cardiac tamponade','Cardiac vein dissection','Cardiac vein perforation','Cardiac ventricular disorder','Cardio-respiratory arrest','Cardio-respiratory arrest neonatal','Cardio-respiratory distress','Cardiogenic shock','Cardiomegaly','Cardiomyopathy','Cardiomyopathy acute','Cardiomyopathy alcoholic','Cardiomyopathy neonatal','Cardiopulmonary failure','Cardiorenal syndrome','Cardiotoxicity','Cardiovascular deconditioning','Cardiovascular disorder','Cardiovascular insufficiency','Cardiovascular syphilis','Carditis','Chest discomfort','Chest pain','Chordae tendinae rupture','Chronic left ventricular failure','Chronic right ventricular failure','Chronotropic incompetence','Clubbing','Complications of transplanted heart','Conduction disorder','Congestive cardiomyopathy','Cor pulmonale','Cor pulmonale acute','Cor pulmonale chronic','Coronary artery aneurysm','Coronary artery dilatation','Coronary artery disease','Coronary artery dissection','Coronary artery embolism','Coronary artery insufficiency','Coronary artery occlusion','Coronary artery perforation','Coronary artery reocclusion','Coronary artery restenosis','Coronary artery stenosis','Coronary artery thrombosis','Coronary bypass thrombosis','Coronary no-reflow phenomenon','Coronary ostial stenosis','Coxsackie carditis','Coxsackie endocarditis','Coxsackie myocarditis','Coxsackie pericarditis','Cyanosis','Cyanosis central','Cytomegalovirus myocarditis','Cytomegalovirus pericarditis','Cytotoxic cardiomyopathy','Diabetic cardiomyopathy','Diastolic dysfunction','Dilatation atrial','Dilatation ventricular','Dissecting coronary artery aneurysm','Dizziness','Dizziness exertional','Dizziness postural','Dressler's syndrome','Dyspnoea','Dyspnoea at rest','Dyspnoea exertional','Dyspnoea paroxysmal nocturnal','Electromechanical dissociation','Endocardial disease','Endocardial fibroelastosis','Endocardial fibrosis','Endocarditis','Endocarditis Q fever','Endocarditis bacterial','Endocarditis candida','Endocarditis enterococcal','Endocarditis fibroplastica','Endocarditis gonococcal','Endocarditis haemophilus','Endocarditis helminthic','Endocarditis histoplasma','Endocarditis meningococcal','Endocarditis noninfective','Endocarditis pseudomonal','Endocarditis rheumatic','Endocarditis staphylococcal','Endocarditis syphilitic','Endocarditis viral','Eosinophilic myocarditis','Extrasystoles','Fluid overload','Foetal arrhythmia','Foetal cardiac disorder','Foetal heart rate deceleration','Foetal heart rate disorder','Fungal endocarditis','Gastrocardiac syndrome','Glycogen storage disease type II','Gravitational oedema','Grey syndrome neonatal','HIV cardiomyopathy','Haemoptysis','Haemorrhage coronary artery','Heart alternation','Heart block congenital','Heart disease congenital','Heart injury','Heart transplant rejection','Heart-lung transplant rejection','Hepatic congestion','Hepatjugular reflux','Holt-Oram syndrome','Hyperdynamic left ventricle','Hyperkinetic heart syndrome','Hypertensive cardiomegaly','Hypertensive cardiomyopathy','Hypertensive heart disease','Hypertrophic cardiomyopathy','In-stent coronary artery restenosis','Interventricular septum rupture','Intracardiac mass','Intracardiac thrombus','Intrapericardial thrombosis','Ischaemic cardiomyopathy','Jugular vein distension','Kearns-Sayre syndrome','Kounis syndrome','Kyphoscoliotic heart disease','Laryngeal dyspnoea','Left atrial dilatation','Left atrial hypertrophy','Left ventricular dysfunction','Left ventricular failure','Left ventricular hypertrophy','Lipomatous hypertrophy of the interatrial septum','Localised oedema','Long QT syndrome','Long QT syndrome congenital','Low cardiac output syndrome','Lown-Ganong-Levine syndrome','Lupus endocarditis','Lupus myocarditis','Malarial myocarditis','Malignant hypertensive heart disease','Malignant pericardial neoplasm','Meningococcal carditis','Microvascular angina','Myocardial abscess','Myocardial calcification','Myocardial depression','Myocardial fibrosis','Myocardial haemorrhage','Myocardial infarction','Myocardial ischaemia','Myocardial oedema','Myocardial reperfusion injury','Myocardial rupture','Myocarditis','Myocarditis bacterial','Myocarditis helminthic','Myocarditis infectious','Myocarditis meningococcal','Myocarditis mycotic','Myocarditis post infection','Myocarditis septic','Myocarditis syphilitic','Myocarditis toxoplasmal','Myoglobinaemia','Myoglobinuria','Myopericarditis','Negative cardiac inotropic effect','Neonatal cardiac failure','Neonatal tachycardia','Nocturnal dyspnoea','Nodal arrhythmia','Nodal rhythm','Non-obstructive cardiomyopathy','Oedema due to cardiac disease','Oedema peripheral','Orthopnoea','Orthostatic intolerance','Ortner's syndrome','Osler's nodes','Pacemaker complication','Pacemaker generated arrhythmia','Palpitations','Papillary muscle disorder','Papillary muscle haemorrhage','Papillary muscle infarction','Papillary muscle rupture','Parasystole','Paroxysmal arrhythmia','Pericardial calcification','Pericardial disease','Pericardial effusion','Pericardial effusion malignant','Pericardial fibrosis','Pericardial haemorrhage','Pericardial neoplasm','Pericardial rub','Pericarditis','Pericarditis adhesive','Pericarditis amoebic','Pericarditis constrictive','Pericarditis

fungal', 'Pericarditis gonococcal', 'Pericarditis helminthic', 'Pericarditis histoplasma', 'Pericarditis infective', 'Pericarditis lupus', 'Pericarditis malignant', 'Pericarditis meningococcal', 'Pericarditis mycoplasma', 'Pericarditis rheumatic', 'Pericarditis syphilitic', 'Pericarditis tuberculous', 'Pericarditis uraemic', 'Peripartum cardiomyopathy', 'Peripheral oedema neonatal', 'Platypnoea', 'Pleuropericarditis', 'Pneumopericardium', 'Positive cardiac inotropic effect', 'Post procedural myocardial infarction', 'Postinfarction angina', 'Postpericardiectomy syndrome', 'Postural orthostatic tachycardia syndrome', 'Presyncope', 'Prinzmetal angina', 'Propofol infusion syndrome', 'Pulmonary artery wall hypertrophy', 'Pulmonary congestion', 'Pulmonary oedema', 'Pulmonary oedema neonatal', 'Purulent pericarditis', 'Radiation pericarditis', 'Rebound tachycardia', 'Reperfusion arrhythmia', 'Restrictive cardiomyopathy', 'Rhabdomyoma', 'Rheumatic fever', 'Rheumatic heart disease', 'Rhythm idioventricular', 'Right atrial dilatation', 'Right atrial hypertrophy', 'Right ventricular dysfunction', 'Right ventricular failure', 'Right ventricular hypertrophy', 'Shoshin beriberi', 'Sick sinus syndrome', 'Silent myocardial infarction', 'Sinoatrial block', 'Sinus arrest', 'Sinus arrhythmia', 'Sinus bradycardia', 'Sinus tachycardia', 'Somatoform disorder cardiovascular', 'Splinter haemorrhages', 'Stress cardiomyopathy', 'Subacute endocarditis', 'Subclavian coronary steal syndrome', 'Subendocardial ischaemia', 'Sudden cardiac death', 'Sudden death', 'Supraventricular extrasystoles', 'Supraventricular tachyarrhythmia', 'Supraventricular tachycardia', 'Syncope', 'Syphilitic endocarditis of heart valve', 'Tachyarrhythmia', 'Tachycardia', 'Tachycardia foetal', 'Tachycardia paroxysmal', 'Torsade de pointes', 'Transfusion-related circulatory overload', 'Trifascicular block', 'Univentricular heart', 'Ventricle rupture', 'Ventricular arrhythmia', 'Ventricular asystole', 'Ventricular dysfunction', 'Ventricular dyskinesia', 'Ventricular extrasystoles', 'Ventricular failure', 'Ventricular fibrillation', 'Ventricular flutter', 'Ventricular hyperkinesia', 'Ventricular hypertrophy', 'Ventricular hypokinesia', 'Ventricular pre-excitation', 'Ventricular remodeling', 'Ventricular septal defect', 'Ventricular septal defect acquired', 'Ventricular tachyarrhythmia', 'Ventricular tachycardia', 'Viral cardiomyopathy', 'Viral myocarditis', 'Viral pericarditis', 'Wandering pacemaker', 'Withdrawal arrhythmia', 'Wolff-Parkinson-White syndrome', 'Wolff-Parkinson-White syndrome congenital')))) ORDER BY ITEM1,EBGM desc

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22483	GI-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/

SUCHITRA M BALAKRISHNAN
01/07/2010

SHARI L TARGUM
01/07/2010

CHRISTINE E GARNETT
01/07/2010

NORMAN L STOCKBRIDGE
01/07/2010



NDA 022483

ACKNOWLEDGE DISPUTE APPEAL

Graceway Pharmaceuticals, LLC
Attention: Jefferson J. Gregory, B.S. Pharm., J.D., H.D.
Chairman and Chief Executive Officer
340 Martin Luther King Jr. Blvd.
Suite 500
Bristol, TN 37620

Dear Mr. Gregory:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyclara (imiquimod) Cream, 3.75%.

We acknowledge receipt on December 16, 2009, of your request for formal dispute resolution concerning the Agency's October 16, 2009, Complete Response letter. You are disputing the requirement to conduct a thorough QT study prior to approval of your NDA.

Your appeal has been forwarded for review to Dr. Julie Beitz, Director, Office of Drug Evaluation III, Center for Drug Evaluation and Research and a response will be provided by January 15, 2010. We will contact you should we have any questions or require additional information.

If you have any questions, please call me at (301) 796-1017.

Sincerely,

{See appended electronic signature page}

Maria R. Walsh, R.N., M.S.
Associate Director for Regulatory Affairs (Acting)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22483	GI-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/

MARIA R WALSH
12/22/2009



NDA 22-483

MEETING MINUTES

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

Dear Dr. Brennan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyclara (imiquimod) Cream, 3.75%.

We also refer to the meeting between representatives of your firm and the FDA on November 17, 2009. The purpose of the meeting was to discuss the October 16, 2009 Complete Response letter for NDA 22-483 Zyclara (imiquimod) Cream, 3.75%.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

{See appended electronic signature page}

Stanka Kukich, M.D.
Deputy Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: Post-Action Guidance Meeting

Meeting Date and Time: November 17, 2009; 1:00pm
Meeting Location: WO Bldg. 22, Rm 1313

Application Number: NDA 22-483
Product Name: Zyclara (imiquimod) Cream, 3.75%
Indication: Actinic Keratosis of the face and/or scalp
Sponsor/Applicant Name: Graceway Pharmaceutical, LLC.

Meeting Chair: Stanka Kukich, M.D.
Meeting Recorder: Kelisha C. Turner

FDA ATTENDEES

Stanka Kukich, M.D., Deputy Director, DDDP
Jill Lindstrom, M.D., Clinical Team Leader, DDDP
Milena Lolic, M.D., Clinical Reviewer, DDDP
Barbara Hill, Ph.D., Pharmacology Supervisor, DDDP
Ida-Lina Diak, Pharm.D., Team Leader, DPV I
Namita Kothary, Pharm.D., Safety Evaluator, DPV I
Barbara Gould, M.B.A.H.C.M., Chief, Project Management Staff, DDDP
Margo Owens, Project Management Team Leader, DDDP
Kelisha C. Turner, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Jefferson Gregory, JD, Chief Executive Officer
James Lee, M.D., Ph.D., Chief Medical Officer
Michael Nordsiek, Executive Vice President, Product Development
John A. A. Bellamy, JD, Executive Vice President and General Counsel
Sean Brennan, Ph.D., Senior Vice President, Regulatory Affairs
Sharon Levy, M.D., Senior Vice President, Clinical Research
TC Meng, M.D., Executive Director, Medical Affairs
Robert Babilon, Senior Director, Product Development
James Kulp, Senior Director, Clinical Research
Tiepu Liu, Senior Director, Biostatistics
Jason Wu, M.D., Senior Director, Clinical Research

(b) (6)

DISCUSSION

Question 1:

Is the Agency's request for a thorough QT study based on the Agency's belief that electrocardiographic studies were not conducted during the development of imiquimod and that therefore the effect of imiquimod on cardiac repolarization and arrhythmias is unknown, or is it based on post-marketing adverse events involving Aldara?

If it is based on post-marketing adverse events involving Aldara can the Agency identify the adverse event?

Response:

The Agency's decision was based on review of the data submitted in NDA 22-483, as well as the postmarketing adverse event database for imiquimod.

Regarding ECG studies:

We are not aware that any ECG studies were conducted as part of the development program for your product, Zyclara, as no ECG data were submitted in your NDA. Please clarify whether you conducted any ECG studies during the development of Zyclara or submitted any ECG data in NDA 22-483. If you did not submit this information in NDA 22-483, please clarify why you did not, as this information was requested in the 74 day letter dated April 1, 2009.

Regarding the safety data base:

Post-marketing events involving imiquimod were reviewed and several concerning cases were identified. **Please see Appendix 1.**

Additional concern was raised within your application. **See Appendix 2.**

Question 2:

Graceway maintains that all of the factors presented above – especially the subnanomolar systemic levels observed in topical studies and the newly reanalyzed electrocardiographic data from Study R837-009, but also the expert opinions from cardiologists – provide sufficient evidence that topically applied imiquimod would not have an effect on cardiac repolarization.

In light of these factors, would the Agency approve NDA 22-483 now (subject to addressing all other issues listed in the Complete Response), and agree that the conduct of a thorough QT study with Holter monitoring can be performed as a post-approval commitment?

Response:

As was stated in the action letter dated October 16, 2009, “[t]he comparative bioavailability of Zyclara and Aldara (used as labeled) is unknown. In the absence of adequate information about the comparative bioavailability of Zyclara relative to Aldara and adequate data demonstrating

that Zyclara does not affect cardiac repolarization, the potential risks of Zyclara are not justified by the potential benefits to patients with actinic keratoses of the face or scalp.”

The current submission does not propose treatment of a new indication and does not propose treatment of a new population. The application proposes a new dosing regimen for the same indication (actinic keratoses) and same population (adults). Actinic keratosis is not a serious or life-threatening condition and many treatment modalities are available. The proposed product does not answer an unmet medical need. The risks of this product have not been fully characterized, especially as related to cardiac function; there is a need for additional data to inform the potential of the product to affect cardiac function.

This information is needed prior to approval of Zyclara.

Question 3:

If question 2 cannot be answered at this time, Graceway respectfully requests that the Agency provide a timeline and the mechanism by which a decision will be reached.

Response:

Not applicable. See above answers.

Meeting Discussion:

The sponsor asked if the Agency agreed that study report R-837-009 was submitted in NDA 22-483. The Agency stated no, we do not agree that a report for this study was submitted in the NDA.

The sponsor asked if resubmission of data from study R-837-009 would be sufficient to adequately address the impact of imiquimod on cardiac repolarization. The Agency responded that we cannot agree that this would be sufficient.

The sponsor stated that they intend to submit a protocol for a TQT study.

General Administrative Comment

Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today’s discussion. Review of information submitted to the IND or NDA might identify additional comments or information requests.

APPENDIX 1

The Post-approval AERS database for imiquimod contains the following cases:

- **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.
- **AERS #3348851; 1999; US;** reported by consumer
A 34-year-old woman with genital warts has applied 2 doses of imiquimod 5%. She left the cream on for about 8 hours before washing it off. Ten minutes after each application she experienced tachycardia that lasted for about 30 minutes.
- **AERS # 3506425; 2000; US;** reported by consumer
A 14-year-old boy with a history of heart murmur used ½ packet of imiquimod 5% daily for common warts on his arms and hands. After using imiquimod for 13 days, he experienced an irregular and rapid heart rate. He stopped using imiquimod, and the reaction abated. He then restarted imiquimod, and the irregular and rapid heart rate returned.
- **AERS # 4191114; 2004; US;** reported by physician
A 71-year-old previously healthy man used imiquimod cream on his nose to treat basal cell carcinoma. He applied the cream three times weekly (wear period unknown). After using imiquimod cream for about 2 months, the patient was found dead. An autopsy was not performed.

APPENDIX 2

From NDA 22-483 subject 01/210 experienced ventricular tachycardia assessed by investigator as non serious event of mild intensity.

- Per received report, patient initially received pharmacologic intervention followed by cardiac ablation for ventricular arrhythmia (type of arrhythmia is poorly specified). It is unclear whether defibrillator was implanted but patient is undergoing assessment every three months (“external cardiac monitoring”). In reviewer’s opinion this event should be included in SAE. Overall, the received report was not detailed enough, but causal relationship to imiquimod could not be excluded.

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

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/s/

STANKA KUKICH
12/03/2009

For Internal Use Only

Meeting Request Granted Form**

(Use this form to document the meeting granted via telephone.)

Complete the information below and check form into DFS.

Application Type	<input type="checkbox"/> P-IND <input type="checkbox"/> IND <input type="checkbox"/> NDA
Application Number	22-483
DATE Sponsor informed of meeting granted	
Sponsor was informed of: <ul style="list-style-type: none"> • date/time & meeting location • expected FDA attendees • meeting briefing package due date • number of copies 	<input type="checkbox"/> Yes 11-16-09 <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes (date: _____) <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Other: please indicate _____
Project Manager	Kelisha Turner

Any follow-up letter must be checked into DFS as an advice letter, **NOT as a meeting request granted letter.

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

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/s/

TISHA L WASHINGTON
11/02/2009

NDA 22483: Medical Officer Memo to File

Subject: 120-Day Safety Update
Medical Officer: Milena Lolic, M.D.
Team Leader: Jill Lindstrom, M.D.
Project manager: Kelisha Turner
Sponsor: Graceway Pharmaceuticals
Drug: Imiquimod cream, 3.75%
Indication: actinic keratosis

Date received: April 19, 2009
Received by reviewer: September 28, 2009
Review completed: September 29, 2009

Regulatory background: Garceway Pharmaceuticals submitted NDA 22483 on December 19, 2009 seeking approval for imiquimod 3.75% cream for AK treatment. On the pre-NDA meeting from October 29, 2008 it was agreed that 120-day safety update should contain updates on the ongoing trials with active moiety as well as on postmarketing experience with 5% imiquimod cream. According to that agreement, applicant's 120-day safety update contains data from 803 study (imiquimod 3.75% cream for AK) and from 801,804 and 805 studies (imiquimod 2.5% and 3.75% for EGW).

Ongoing studies with imiquimod 2.5% and 3.75% cream:

1. Study GW01-0803 entitled "A follow-up study to evaluate sustained clearance rates of actinic keratosis up to one year after completion of studies GW01-0702, GW01-0703, GW01-0704, and GW01-0702" started on April 30, 2008. As of March 25, 2009 195 subjects were enrolled and none of the subjects reported related SAEs or was discontinued due to related AE.

As per protocol, no new laboratory data were collected.

There are 8 subjects that reported local adverse events and those are summarized below:

Patient No.	Previous Phase 3 Study Number	Previous Treatment	Adverse Event	Serious and Related
01-213	GW01-0702	2.5% imiquimod	squamous cell carcinoma	No
04-208	GW01-0702	placebo	Seborrheic dermatitis	No
08-206	GW01-0702	3.75% imiquimod	residual scar on forehead	No
19-321	GW01-0703	3.75% imiquimod	Superficial verrucous SCC	No
36-417	GW01-0704	2.5% imiquimod	Seborrheic dermatitis	No
38-448	GW01-0704	2.5% imiquimod	Pruritus	No
47-502	GW01-0705	3.75% imiquimod	BCC	No
47-540	GW01-0705	3.75% imiquimod	BCC	No

Source: Table 2 from Applicant's 120-day Safety Update Report

2. Imiquimod cream formulations 2.5% and 3.75% are being studied for the treatment of (b) (4). As of the reporting cut-off date of March 25, 2009 there were no adverse events reported that were considered serious, related to study product and unexpected.

Post-marketing safety data for imiquimod 5% cream:

Safety information collected for imiquimod 5% (Aldara cream) is included in Periodic ADE Report submitted to NDA 20-723 on April 24, 2009. There were 12 initial 15-day AEs and 668 initial non-15-day AEs reported from February 27, 2008 through February 26, 2009. There were also follow up reports and those include one 15-day and three non-15 day reports. Applicant did not recommend any changes to Aldara cream label based on these AEs that occurred from February 27, 2008 through February 26, 2009.

However, applicant's periodic review of Aldara cream safety data base identified several adverse events as clinically important (based on the cumulative frequency) therefore applicant recommends the following changes to the Aldara cream label in section 6.5

Post marketing Experience:

Application site disorders: tingling at the application site,

Gastro-intestinal System Disorders: abdominal pain,

Musculo-Skeletal System Disorders: arthralgia, and

Infections and Infestations: herpes simplex.

Conclusion: The review of 120-day safety update for imiquimod did not reveal any new safety signal in ongoing studies with imiquimod 3.75% cream. However, the review of postmarketing safety data for imiquimod 5% cream reveals new safety concerns that will require labeling changes for Aldara cream. Consequently, these changes will be discussed with applicant during labeling negotiations for imiquimod 3.75% cream.

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/

MILENA M LOLIC
10/15/2009

JILL A LINDSTROM
10/15/2009



NDA 022483

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Graceway Pharmaceuticals, LLC
340 Martin Luther King Jr. Boulevard
Bristol, Tennessee 37620

ATTENTION: Sean Brennan
Vice President, Regulatory Affairs

Dear Dr. Brennan:

Please refer to your New Drug Application (NDA) dated December 19, 2008, received December 19, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for imiquimod cream, 3.75%.

We also refer to your submission dated July 7, 2009, requesting formal dispute resolution concerning the June 12, 2009, "Proprietary Name Request – Unacceptable" decisional letter from the Division of Medication Error Prevention and Analysis (DMEPA) regarding the proposed proprietary name, Zyclara, for imiquimod cream (3.75% strength). Your July 7, 2009 letter disputed the June 12, 2009 position expressed by DMEPA regarding the unacceptability of the proposed proprietary name, Zyclara, for pending NDA 022483.

We also refer to your submissions dated July 17 and July 20, 2009, both received on July 21, 2009, in which you documented Graceway's decision to pursue reconsideration by DMEPA and the Division of Dermatology and Dental Products of the initial "unacceptable" decision regarding the proposed proprietary name, Zyclara.

We have completed our review of the information provided in your July 7, 2009 submission and do not object to the proposed proprietary name because of its similarity in spelling or pronunciation to another proprietary name or the established name of a different drug or ingredient (i.e., orthographic or phonetic similarity), or from a promotional perspective. Therefore, we have determined that the proposed proprietary name, Zyclara, is acceptable for the imiquimod 3.75% cream product.

Consistent with standard practice, the proposed proprietary name, Zyclara, will be re-reviewed if this NDA is not approved on or before the October 19, 2009 goal date. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your March 13, 2009, submission are altered prior to approval of the marketing application, the proposed proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet L. Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application contact the Regulatory Project Manager in the Division of Dermatology and Dental Products, Kelisha Turner at (301) 796-2110.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

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/s/

CAROL A HOLQUIST
10/07/2009

Frost, Kathleen R

From: Frost, Kathleen R
Sent: Tuesday, September 29, 2009 4:21 PM
To: Hankin, Joan E; Dal Pan, Gerald; Beitz, Julie G; Broder-Feldman, Elena; Holquist, Carol A
Cc: Piazza Hepp, Toni D; Anderson, Janet
Subject: Zyclara Reconsideration Letter

I called Sean Brennan at Graceway this afternoon at (423) 274-5210 to apologize for our delay in issuing the letter on the acceptability of the name Zyclara for NDA 22-483 (imiquimod cream). I explained that we had anticipated issuing the letter sooner, but due to staff absences it has taken longer than we thought. I assured him that in my discussion with him about using reconsideration rather than a formal dispute resolution request, I was not intentionally misleading him on the timeframe. He said that one reason that they are anxious for our letter is that they are hoping to use the same name in Canada, and Health Canada had asked for documentation of the acceptability of the name in the U.S. He also asked why this letter involved so much clearance. I said that since this is a new process, letters are setting precedents, and we are being careful with the wording so that we don't have unintended consequences down the line. He said that's what they assumed. He did ask if the letter was still going to allow them to use the name, and I said that yes, with the standard caveats about the acceptability of a proposed name. He said he'd seen that standard language before. He thanked me for the call.

I'll document this tcon in DARRTS.

-Kathleen

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

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/s/

KATHLEEN R FROST
10/16/2009



Shari L. Targum, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993
Tel (301) 796-1151

Memorandum

DATE: September 15, 2009

FROM: Shari L. Targum, M.D., Team Leader
Division of Cardio-Renal Drug Products, HFD-110

THROUGH: Norman Stockbridge, M.D., Ph.D., Director
Division of Cardio-Renal Drug Products, HFD-110

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

SUBJECT: NDA 22-483

NAME OF DRUG: Imiquimod cream, 3.75%

TRADE NAME: N/A

FORMULATION: (b) (4)

RELATED APPLICATIONS: N/A

APPROVED INDICATIONS: N/A

SPONSOR: Graceway Pharmaceuticals, LLC

DOCUMENTS AVAILABLE FOR REVIEW: 1. Consult request; 2. NDA 22-483 (edr) 12/24/2008

DATE CONSULT RECEIVED: September 1, 2009

DESIRED COMPLETION DATE: September 21, 2009

DATE CONSULT COMPLETED: September 17, 2009

REASON FOR CONSULTATION:

1. What is our assessment of imiquimod as potential proarrhythmic drug?
2. What would be the best way to address the review division's concern related to imiquimod and arrhythmias?

BACKGROUND:

Imiquimod 5% cream was initially approved for marketing in 1997. The sponsor is seeking approval for a 3.75% strength with a new dosing regimen (more frequent application to a larger surface area) for the treatment of actinic keratoses.

Imiquimod is a toll-like receptor (TLR) agonist. Although its mechanism of action is not elucidated, imiquimod appears to mediate its effects via activation of TLR7. According to Dr. Lolic, there is systemic exposure with highly variable concentrations.

According to the review division:

1. Imiquimod caused cardiac stimulation in dogs and had stimulatory effects on guinea pig cardiac tissue. (Per Dr. Lolic, there were data from the original NDA about 20 years ago that imiquimod was associated with an increase in heart rate).
2. Resiquimod, a related compound in development, (b) (4)
3. Sotirimod, a related compound in development, (b) (4)

According to the NDA submission, the Agency agreed that no additional nonclinical studies would be required to support the development of the new formulation.

Summary of clinical findings:

1. There are no ECG data available from the imiquimod development program;
2. One subject in the current development program developed unexplained ventricular tachycardia.

Postmarketing database (5% cream):

1. Two cases of (?SV) tachycardia and one case of SVT, all with positive re-challenge;
2. One case of sudden death in a previously healthy 71 year-old man.

COMMENTS:

1. Assessment of imiquimod as a proarrhythmic drug:

The issue is whether imiquimod is associated with cardiovascular effects or mechanisms that lead to arrhythmias (supraventricular or ventricular). The postmarketing cases with positive re-challenge imply a temporal relationship; however, it is not clear whether other factors were also at play. The available clinical data are scant and do not allow for conclusions.

2. Additional thoughts/evaluation:

1. You should review the available postmarketing experience with regard to arrhythmias, syncope, palpitations, seizures and sudden death. You should also review the current NDA submission regarding size of safety database, extent of drug exposure, and expected background event rates in the study population.
2. In an elderly population, as in the 71 year-old man, it is difficult to know whether a single case of sudden death is due to the drug, undiagnosed heart disease, or the “play of chance.”
3. For the case of “unexplained ventricular tachycardia,” your Division should review the ECG tracing, drug dosing (concentrations if available), and clinical evaluation (e.g., laboratory tests if any).
4. A key question is whether the new formulation will lead to an increase in systemic exposure compared to the old formulation that has been used for the past 20 years.
5. If the new formulation will lead to the potential of higher systemic exposures, you could certainly make a case for additional testing, such as a thorough QT (TQT) study and preclinical testing to evaluate effects on ion channels and electrophysiology. Besides evaluating the QT interval, a TQT study would reveal concentration-related effects on heart rate.

Thank you. If you have any further questions, please feel free to contact me or the Division.

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/

SHARI L TARGUM
09/17/2009

NORMAN L STOCKBRIDGE
09/17/2009

REQUEST FOR CONSULTATION

TO (Office/Division):
Division of Cardiovascular and Renal Products
Devi Kozeli, Project Manager

FROM (Name, Office/Division, and Phone Number of Requestor):
Milena Lolic, M.D. 301-796-3825
Jill Lindstrom, M.D., Team Leader 301-796-0944
Kelisha Turner, Regulatory Project Manager
301-796-0766
Division of Dermatology and Dental Products

DATE August 31, 2009	IND NO.	NDA NO. 22-483	TYPE OF DOCUMENT Original NDA	DATE OF DOCUMENT December 19, 2009
NAME OF DRUG Tradename (imiquimod) Cream, 3.75%	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG 5	DESIRED COMPLETION DATE September 21, 2009	

NAME OF FIRM: Graceway Pharmaceuticals, LLC.

REASON FOR REQUEST

I. GENERAL

- | | | |
|----------------------------------------------------------|--------------------------------------------------|------------------------------------------------------------|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|-------------------------------------------------|-------------------------------------------------|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--------------------------------------------------|------------------------------------------------------|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|----------------------------------------------|--------------------------------------|
| <input checked="" type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|----------------------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: DDDP is concerned about pro-arrhythmic potential of imiquimod cream.

Imiquimod 5% cream was initially approved for marketing in 1997. The sponsor now seeks approval for a 3.75% strength with a new dosing regimen (more frequent application to larger surface area) for the treatment of actinic keratoses.

Summary of nonclinical findings:

1. Imiquimod caused cardiac stimulation in dogs and had stimulatory effects on guinea pig cardiac tissue.
2. Resiquimod, a related compound in development, (b) (4)
3. Sotirimod, a related compound in development, (b) (4)

Summary of clinical findings:

1. Clinical trials database (3.75% cream):
 - a. One subject in the current development program developed unexplained ventricular tachycardia.
 - b. There are no clinical EKG data available from the imiquimod development program.
2. Postmarketing database (5% cream):
 - a. Two cases of (?SV) tachycardia and one case of SVT, all with positive re-challenge.
 - b. One case of sudden death in previously healthy 71 year-old man.

We seek your input on the following questions:

1. What is your assessment of imiquimod as potential pro-arrythmogenic drug?
2. What would be the best way to address our concern related to imiquimod and arrhythmias?

This submission is available in the EDR.

SIGNATURE OF REQUESTOR

Milena Lolic, M.D.

Jill Lindstrom, M.D.

Kelisha Turner

METHOD OF DELIVERY (Check one)

DFS

EMAIL

MAIL

HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22483	----- ORIG 1	----- GRACEWAY PHARMACEUTICA LS LLC	----- IMIQUIMOD 3.75% CREAM

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/s/

KELISHA C TURNER
08/31/2009



NDA 22-483

**FORMAL DISPUTE RESOLUTION REQUEST
ACKNOWLEDGEMENT OF WITHDRAWAL**

Graceway Pharmaceuticals, LLC
340 Martin Luther King Jr. Boulevard
Bristol, Tennessee 37620

ATTENTION: Jefferson J. Gregory, B.S. Pharm., J.D., H.D.
Chairman and Chief Executive Officer

Dear Dr. Gregory:

Please refer to your New Drug Application (NDA) dated December 19, 2008, received December 19, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for imiquimod cream, 3.75%.

We acknowledge receipt on July 7, 2009, of your July 7, 2009 letter, addressed to Susan Walker, M.D., Director of the Division of Dermatology and Dental Products (DDDP) in the Office of New Drugs, requesting formal dispute resolution concerning the Agency's June 12, 2009, "Proprietary Name Request – Unacceptable" letter to NDA 22-483 (imiquimod cream, 3.75%), which was signed by Carol Holquist, R.Ph., Director of the Division of Medication Error Prevention and Analysis (DMEPA) in the Office of Surveillance and Epidemiology. In your July 7, 2009 correspondence, you disputed the position expressed by DMEPA.

In a teleconference on July 16, 2009 with Sean Brennan, Ph.D., Vice President, Regulatory Affairs, I informed Dr. Brennan that we did not believe that Graceway Pharmaceuticals, LLC (Graceway), DMEPA and DDDP had completed discussions of the issues that Graceway had raised in the formal dispute resolution request submitted on July 7, 2009, and encouraged Graceway to bring the matter to DMEPA and DDDP for reconsideration rather than pursuing formal dispute resolution. In a July 17, 2009 teleconference, Dr. Brennan informed me that Graceway would pursue reconsideration at this time as opposed to the request for formal dispute resolution. We acknowledge your letters dated July 17 and July 20, 2009, both received on July 21, 2009, documenting that decision.

The Agency considers your formal dispute resolution request, dated July 7, 2009, withdrawn. After the reconsideration process is completed at the division level, you may submit a request for formal dispute resolution, if you choose to do so.

If you have any questions regarding the contents of this letter, or any other aspects of the proprietary name review process, please call Janet L. Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application, contact Kelisha Turner, Regulatory Project Manager in the Division of Dermatology and Dental Products at (301) 796-2110.

Sincerely,

{See appended electronic signature page}

Kathleen R. Frost
Associate Director for Regulatory Affairs
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22483	----- GI 1	-----	----- IMIQUIMOD 3.75% CREAM

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/s/

KATHLEEN R FROST
08/05/2009

Turner, Kelisha C

From: Greeley, George
Tuesday, July 07, 2009 3:28 PM
To: Turner, Kelisha C
Cc: Stowe, Ginneh D.
Subject: NDA 22-483 Imiquimod
Importance: High

Hi Kelisha,

The Imiquimod full waiver was reviewed by the PeRC PREA Subcommittee on June 24, 2009. The Division recommended a full waiver because necessary studies would be impossible or highly impracticable because there are too few children with disease/condition to study. The PeRC agreed with the Division to grant a full waiver for this product.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs
FDA/CDER
10903 New Hampshire Ave.
Bldg #22, Room 6467
Silver Spring, MD 20993-0002
1.796.4025

 Please consider the environment before printing this e-mail.



NDA 22-483

INFORMATION REQUEST LETTER

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

Dear Dr. Brennan:

Please refer to your December 19, 2008 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tradename (imiquimod) Cream, 3.75%.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Chemistry, Manufacturing, and Controls:

1. Amend the presentation of your trade name, established name, dosage form, and strength in all container/closure systems as follows:

Trade Name
(imiquimod) Cream
3.75%

2. Update the following information on all container/closure systems.
 - a. NDA number
 - b. Net weight per packet
 - c. Storage temperature
3. Provide the color mock ups of the container/closures with indicated changes.

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

Sincerely,

{See appended electronic signature page}

Barbara Gould, M.B.A.H.C.M.
Chief, Project Management Staff
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Sue Kang
6/26/2009 04:16:34 PM
Signing on behalf of Barbara Gould



NDA 22-483

INFORMATION REQUEST LETTER

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

Dear Dr. Brennan:

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

We are reviewing your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Clinical Pharmacology:

As part of the review of the performance of the assay, the Clinical Pharmacology reviewer would like to obtain a better understanding of your analytical method-so as to validate its performance, especially in light of the results (ie, the BLQ nature of the results). Specifically please supply the following documents, as referenced in your analytical study report:

The page numbers refer to your PDF file gw01-0706.PDF

(b) (4) Validation report V080216 (refer to Page 530)

Analytical method M080216 (refer to Page 531)

(b) (4) Validation Report for 9196.97 (refer to Page 531, last paragraph)

(b) (4) Validation Report for 9196.91 (refer to Page 531, last paragraph)

(b) (4) Validation Report for 9196.38 (refer to Page 531, last paragraph)

Please officially submit this information to your NDA no later than July 1, 2009.

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

Sincerely,

{See appended electronic signature page}

Margo Owens
Team Leader, Project Management Staff
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margo Owens
6/18/2009 04:22:51 PM



NDA 22-483

**PROPRIETARY NAME REQUEST
- UNACCEPTABLE**

Graceway Pharmaceuticals, LLC
340 Martin Luther King Jr. Boulevard
Bristol, Tennessee 37620

ATTENTION: Sean Brennan, PhD
Vice President, Regulatory Affairs

Dear Dr. Brennan:

Please refer to your New Drug Application (NDA) dated December 19, 2008, received December 19, 2008, submitted under section 505(b) of the Federal, Food, Drug, and Cosmetic Act for Imiquimod cream, 3.75%.

We also refer to your March 13, 2009 correspondence, received March 16, 2009, requesting review of your proposed proprietary name, Zyclara. We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

Your proposal to use a different proprietary name, Zyclara, for a product containing the same active ingredient, Imiquimod, contained in another product you market, Aldara (Imiquimod Cream 5%) introduces an added safety risk of inadvertent concomitant therapy in patients being treated by different providers for different dermatologic conditions. The three indications of use for which Imiquimod is approved (actinic keratosis, superficial basal cell carcinoma, and external genital warts) can co-occur in individual patients. This concomitant therapy could go undetected by the treating physicians, the dispensing pharmacist(s) and most importantly, by the patient, who may be unaware that 'Aldara' and 'Zyclara' contain the same active ingredient. By unknowingly treating both conditions simultaneously with the same active ingredient, there is a safety risk of systemic exposure to Imiquimod, which may result in the following adverse events cited in the approved product labeling: headache, upper respiratory infections, influenza-like symptoms and myalgia. Additionally, Aldara and Zyclara have an overlapping indication of use, actinic keratosis. It is possible that a patient may be treated for the same indication of use by different prescribers. The use of the same active ingredient may go undetected because the dosing regimen for this indication of use is different between products. Aldara recommends a twice weekly application whereas Zyclara recommends a daily application at bedtime. In either scenario, the over use of Imiquimod could increase the occurrence of adverse reactions already associated with Imiquimod use including localized skin reactions.

Additionally, our evaluation determined that the potential for product confusion and medication errors identified in your justification for separate labeling is unfounded. The rationale for separate labeling cited variations in the two treatment regimens, indications of use, treatment areas, and frequency of use and duration of use as reasons to support the use of a different name. The errors you have described in support of the use of a different proprietary name already exist with your currently marketed product. Thus these errors could occur independent of the use of different proprietary names between the two Imiquimod strengths.

We note that you have proposed an alternate proprietary name, (b) (4) in your submission dated March 13, 2009. However, based on the findings of this review, (b) (4) will also be unacceptable for the aforementioned reasons. We request that you submit revised labels and labeling that reflects the proprietary name Aldara and product information for both the 5% and 3.75% strengths.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Janet L. Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application contact Kelisha Turner, Regulatory Project Manager in the Division of Dermatology and Dental Products at (301) 796-2110.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

Carol Holquist
6/12/2009 04:31:24 PM

REQUEST FOR CONSULTATION

TO (*Office/Division*): Office of Surveillance and Epidemiology
Janet Anderson
WO 22, Room 3435

FROM (*Name, Office/Division, and Phone Number of Requestor*):
Milena Lolic, M.D., Clinical Reviewer
Jill Lindstrom, M.D., Clinical Team Leader (CDTL)
Kelisha Turner, RPM, DDDP, 301-796-0766

DATE
June 5, 2009

IND NO.

NDA NO.
22-483

TYPE OF DOCUMENT
Original NDA

DATE OF DOCUMENT
December 19, 2008

NAME OF DRUG
Tradename (imiquimod)
Cream, 3.75%

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
5

DESIRED COMPLETION DATE
August 1, 2009

NAME OF FIRM: Graceway Pharmaceuticals, LLC.

REASON FOR REQUEST

I. GENERAL

- | | | |
|----------------------------------------------------------|--------------------------------------------------|---------------------------------------------------------------------|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|----------------------------------------------------------|----------------------------------------------------------|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>): |
| <input type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>): | |

III. BIOPHARMACEUTICS

- | | |
|--------------------------------------------------|------------------------------------------------------|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (<i>List below</i>) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|----------------------------------------------|--------------------------------------|
| <input checked="" type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|----------------------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: DDDP has received an original NDA submission for NDA 22-483, Tradename (imiquimod) Cream, 3.75% for actinic keratosis. Imiquimod is a topical immune response modifier currently approved under the name Aldara 5% for 3 dermatologic indications (genital warts in 1997, basal cell CA and limited area AK in 2004).

Safety concern is raised for the following reasons:

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

2

(b) (4)

We have consulted the Division of Cardiovascular and Renal Products regarding the effect of imiquimod on the cardiac system. In the response, the reviewer is recommending that we also consult OSE in this regard.

Our question is:

How does the incidence of cardio-vascular events in the imiquimod treatment population compare with that of the general population?

The original submission is available electronically in the EDR.

Thank you.

SIGNATURE OF REQUESTOR

Kelisha Turner, RPM

METHOD OF DELIVERY (Check one)

DFS

EMAIL

MAIL

HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Kelisha Turner

6/8/2009 05:17:41 PM



NDA 22-483

INFORMATION REQUEST LETTER

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

Dear Dr. Brennan:

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

We are reviewing your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Clinical:

1. Provide all of the available data about subject 51/539 from study GW01-0705 who developed pancytopenia and non-Hodgkin's lymphoma.
2. Provide data on the 15 subjects (6 from pivotal and 9 from supportive studies) who had lymphadenopathy reported as a treatment related adverse event. In particular, provide the location of the lymphadenopathy and hematological data.

Pharmacology/Toxicology:

The quantitative information of the impurity [REDACTED] ^{(b) (4)} in the drug product that was used in clinical studies and toxicology studies is needed for safety assessment and was requested previously. In addition, in your CMC response that was received by FDA on 05/01/09, you stated that impurity [REDACTED] ^{(b) (4)} is a major metabolite in *in vitro* metabolic studies using human liver microsomes. Provide quantitative information of the presence of [REDACTED] ^{(b) (4)} in the metabolic profiles of imiquimod in animals that were used in toxicology studies and carcinogenicity studies.

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

Sincerely,

{See appended electronic signature page}

Margo Owens
Team Leader, Project Management Staff
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margo Owens

6/1/2009 02:52:33 PM



NDA 22-483

INFORMATION REQUEST LETTER

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

Dear Dr. Brennan:

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

We are reviewing your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Clinical:

1. Clarify why the subject from GW01-0704 trial (01/210) who had ventricular tachycardia listed as AE, was not included in the serious adverse event category.
2. Provide any new information, if available, about Subject 17/302 from trial GW01-0703 who died 3 weeks after completing the trial.
3. Subject 05/206 from trial GW01-0702 developed tremors that lasted from day 29-38 and the study drug was discontinued (16.2.7.5). Clarify whether the subject was discontinued from the study (information not included in 14.3.3). Provide the case report forms for this subject.

CMC:

1. Identify the age of batch GM7713 (Expiration: 30 Apr 2009) when it was used in the clinical studies.
2. You are proposing a 24 month expiration dating period at (b)(4) 25⁰C for the drug product. However, the (b)(4) stability data are not provided in the NDA to support the storage at refrigerated condition. Provide stability data generated at (b)(4) C per ICH Q1A (R2). Additionally, amend the post approval stability protocol by including the (b)(4) storage condition.
3. A very limited amount of long term stability data is provided in the NDA. Amend the stability section of the NDA with additional data you have collected since the NDA submission to justify the 24 month of expiration dating period.

Pharmacology/Toxicology:

1. To date, the pharmacology/toxicology information request that was relayed to you in the NDA filing letter has not been addressed. Please provide the following information:

Quantitative information for the new impurity (most likely (b) (4)) in the clinical and toxicology test materials.

Biostatistics:

1. In regards to the dataset AD_OPS for Study GW01-0704:

- Clarify why Subject 38/409 has two entries, as this dataset is supposed to have only one record per subject.
- Clarify why the two records for Subject 38/409 have different values for the variable AUCLSR (444.5 vs 407.0) and identify the correct value of AUCLSR for this subject.
- Provide a detailed algorithm or statistical program for calculating the variable AUCLSR.

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

Sincerely,

{See appended electronic signature page}

Margo Owens
Team Leader, Project Management Staff
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margo Owens

5/14/2009 05:35:39 PM

Turner, Kelisha C

From: Turner, Kelisha C
Sent: Wednesday, April 22, 2009 4:27 PM
To: 'Sean Brennan'
Cc: Owens, Margo
Subject: NDA 22-483 - Tradename (imiquimod) Cream, 3.75% - Information Request

Attachments: HighlightsofClinicalPharmacology.doc

Dear Dr. Brennan,

Please refer to your NDA 22-483 for Tradename (imiquimod) Cream, 3.75%. The Agency has the following request for information:

- Complete the attached "Highlights of Clinical Pharmacology" table and submit the completed copy to your NDA.



HighlightsofC
calPharmacol

Response is requested as soon as possible. Please contact me with any questions.

Sincerely,

Kelisha C. Turner
Regulatory Health Project Manager
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration

Tel: 301-796-0766
Fax: 301-796-9894
kelisha.turner@fda.hhs.gov

Highlights of Clinical Pharmacology

Therapeutic dose	Include maximum proposed clinical dosing regimen.	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) C _{max} and AUC
	Multiple Dose	Mean (%CV) C _{max} and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	T _{max}	<ul style="list-style-type: none"> • Median (range) for parent • Median (range) for metabolites
Distribution	V _d /F or V _d	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated • Other routes
	Terminal t _{1/2}	<ul style="list-style-type: none"> • Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in C _{max} and AUC
	Sex	Specify mean changes in C _{max} and AUC
	Race	Specify mean changes in C _{max} and AUC
	Hepatic & Renal Impairment	Specify mean changes in C _{max} and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in C _{max} and AUC
	Food Effects	Specify mean changes in C _{max} and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical	Describe worst case scenario and expected fold-change in C _{max} and	

Exposure Scenario

AUC. The increase in exposure should be covered by the supra-therapeutic dose.

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/s/

Kelisha Turner
5/5/2009 11:04:34 AM
CSO

Kelisha Turner
5/5/2009 11:05:10 AM
CSO

Request for Biopharmaceutical Inspections

DATE: April 17, 2009

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

THROUGH: Kelisha C. Turner
Regulatory Project Manager, HFD-540

FROM: Dennis Bashaw, Pharm.D.
Director, Division of Clinical Pharmacology III

SUBJECT: Request for Biopharmaceutical Inspections
NDA 22-483
Imiquimod 3.75% Cream.

The following studies/sites pivotal to approval have been identified for inspection:

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

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
GW01-0706	Melanie C. Fein, MD Comprehensive Phase One TM 3745 Broadway, Suite 100 Fort Myers, FL 33901 (239)461-8600	(b) (4) 

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by July 15th, 2009. We intend to issue an action letter on this application by Sept. 1, 2009.

Should you require any additional information, please contact Kelisha C. Turner (kelisha.turner@fda.hhs.gov)

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/s/

Dennis Bashaw
4/23/2009 10:06:25 AM
BIOPHARMACEUTICS

REQUEST FOR CONSULTATION

TO (Office/Division): Division of Cardiovascular and Renal Products
Devi Kozeli, Project Manager

FROM (Name, Office/Division, and Phone Number of Requestor):
Milena Lolic, M.D. 301-796-3825
Jill Lindstrom, M.D., Team Leader 301-796-0944
Kelisha Turner, Regulatory Project Manager 301-796-0766
Division of Dermatology and Dental Products

DATE
April 20, 2009

IND NO.

NDA NO.
22-483

TYPE OF DOCUMENT
Original NDA

DATE OF DOCUMENT
December 19, 2009

NAME OF DRUG
Tradename (imiquimod)
Cream, 3.75%

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
5

DESIRED COMPLETION DATE
May 20, 2009

NAME OF FIRM: Graceway Pharmaceuticals, LLC.

REASON FOR REQUEST

I. GENERAL

- | | | |
|----------------------------------------------------------|--------------------------------------------------|------------------------------------------------------------|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|-------------------------------------------------|-------------------------------------------------|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--------------------------------------------------|------------------------------------------------------|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|----------------------------------------------|--------------------------------------|
| <input checked="" type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|----------------------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: 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). In NDA 22-483, the applicant seeks approval of imiquimod 3.75% cream for the treatment of actinic keratosis using a more intensive dosing regimen. 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, we have 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, 2) (b) (4) nd
3) No EKG studies were done in imiquimod development program.

We seek your input on the following questions:

Has the applicant adequately addressed the potential of their product to impact cardiac repolarization? Are additional data needed to address the potential for QT/QTc interval prolongation? Are there any additional studies needed to address the effect of imiquimod on cardiac system?

NDA 22-483 is an electronic submission and may be accessed at http://edr.fda.gov:7777/edr/EDR_Main.jsp

Thank you.

SIGNATURE OF REQUESTOR

Milena Lolic, M.D.

Jill Lindstrom, M.D.

Kelisha Turner

METHOD OF DELIVERY (Check one)

DFS

EMAIL

MAIL

HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Kelisha Turner

4/20/2009 03:23:52 PM

NDA/BLA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

Application Information		
NDA # 22-483 BLA#	NDA Supplement #:S- N/A BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Tradename Established/Proper Name: (imiquimod) Dosage Form: Cream Strengths: 3.75%		
Applicant: Graceway Pharmaceuticals, LLC Agent for Applicant (if applicable): N/A		
Date of Application: December 19, 2008 Date of Receipt: December 19, 2008 Date clock started after UN: N/A		
PDUFA Goal Date: October 19, 2009	Action Goal Date (if different):	
Filing Date: February 17,2009 Date of Filing Meeting: January 30, 2009		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed Indication(s): AK face &/or scalp		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>Refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical disease Priority review voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/> Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR	

601.42)	
Collaborative Review Division (if OTC product): N/A	
List referenced IND Number(s): IND 30,432; IND 49,480; IND 49,464	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ora/compliance_ref/aiplist.html If yes, explain: If yes, has OC/DMPQ been notified of the submission? Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status Comments:	<input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
Exclusivity	

<p>Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</i></p> <p>If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES # years requested: 3 <input type="checkbox"/> NO
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<input checked="" type="checkbox"/> Not applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
<ol style="list-style-type: none"> 1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)). 3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? 	<input checked="" type="checkbox"/> Not applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>	
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<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <i>Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</i></p>		<input type="checkbox"/> YES <input type="checkbox"/> NO	
<p>If yes, please list below:</p>			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>			
Format and Content			
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p>Comments:</p>		<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input checked="" type="checkbox"/> Mixed (CTD/non-CTD)	
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>		<p>N/A</p>	
<p>If electronic submission: <u>paper</u> forms and certifications signed (non-CTD) or <u>electronic</u> forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3397), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p>Comments:</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
<p>If electronic submission, does it follow the eCTD guidance? (http://www.fda.gov/cder/guidance/7087rev.pdf)</p> <p>If not, explain (e.g., waiver granted): Waiver granted 4/8/08 via email. Hybrid.</p>		<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO	

<p>Form 356h: Is a signed form 356h included?</p> <p><i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Index: Does the submission contain an accurate comprehensive index?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Controlled substance/Product with abuse potential:</p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BLAs/BLA efficacy supplements only:</p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Patent Information (NDAs/NDA efficacy supplements only)	
<p>Patent information submitted on form FDA 3542a?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Debarment Certification	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, both the applicant and the U.S. Agent must</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>sign the certification.</p> <p><i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p> <p>Comments: Correction in 1-30-09 submission.</p>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Financial Disclosure	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Pediatrics	
<p><u>PREA</u></p>	
<p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	
<p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p>
<p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> • <i>If no, request in 74-day letter.</i> • If yes, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) 	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p>Comments:</p>	

BPCA (NDAs/NDA efficacy supplements only):	
Is this submission a complete response to a pediatric Written Request? <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i> Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Prescription Labeling	
Check all types of labeling submitted. Comments:	<input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
Is electronic Content of Labeling submitted in SPL format? <i>If no, request in 74-day letter.</i> Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Package insert (PI) submitted in PLR format? If no , was a waiver or deferral requested before the application was received or in the submission? If before , what is the status of the request? <i>If no, request in 74-day letter.</i> Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
REMS consulted to OSE/DRISK? Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP? Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

OTC Labeling	
<p>Check all types of labeling submitted.</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Meeting Minutes/SPA Agreements	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments: IND 30,432 - 1/20/08 (b) (4)</p>	<input checked="" type="checkbox"/> YES Date(s): <input type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments: IND 49,480 - 10/29/08</p>	<input checked="" type="checkbox"/> YES Date(s): <input type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p>Comments: IND 49,480 - 3/30/01;Response to Request</p>	<input checked="" type="checkbox"/> YES Date(s): <input type="checkbox"/> NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 30, 2009

NDA/BLA #: NDA 22-483

PROPRIETARY/ESTABLISHED NAMES: Tradename (imiquimod) Cream, 3.75%

APPLICANT: Graceway Pharmaceuticals, LLC.

BACKGROUND: The proposed indication, TRADENAME Cream, 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.

(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kelisha Turner	Y
	CPMS/TL:	Margo Owens	Y
Cross-Discipline Team Leader (CDTL)	Jill Lindstrom, M.D.		Y
Clinical	Reviewer:	Milena Lolic, M.D.	Y
	TL:	Jill Lindstrom, M.D.	Y
Social Scientist Review <i>(for OTC products)</i>	Reviewer:	N/A	
	TL:		
Labeling Review <i>(for OTC products)</i>	Reviewer:	N/A	
	TL:		
OSE	Reviewer:	Nancy Carothers	Y

	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:		

Clinical Pharmacology	Reviewer:	Edward Bashaw, Pharm.D	Y
	TL:	Edward Bashaw, Pharm.D	Y
Biostatistics	Reviewer:	Kathleen Fritsch, Ph. D	Y
	TL:	Mohamed Alosh, Ph.D	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Jianyong Wang, Ph.D	Y
	TL:	Barbara Hill, Ph.D	Y
Statistics, carcinogenicity	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Rajiv Agarwal, Ph.D	Y
	TL:	Shulin Ding, Ph.D	Y
Facility (<i>for BLAs/BLA supplements</i>)	Reviewer:	N/A	
	TL:		
Microbiology, sterility (<i>for NDAs/NDA efficacy supplements</i>)	Reviewer:	N/A	
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Roy Blay	Y
	TL:		
Other reviewers			

OTHER ATTENDEES:

505(b)(2) filing issues? If yes, list issues:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Per reviewers, are all parts in English or English translation? If no, explain:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>Electronic Submission comments</p> <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
BIOSTATISTICS Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments: Per Rajiv Agarwal, 1/30/09.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Sterile product? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p>If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>FACILITY (BLAs only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Susan J. Walker, M.D., F.A.A.D.</p> <p>GRMP Timeline Milestones:</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	<p>The application is unsuitable for filing. Explain why:</p>
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input type="checkbox"/>	<p>Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.</p>
<input type="checkbox"/>	<p>If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.</p>
<input type="checkbox"/>	<p>If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.</p>
<input type="checkbox"/>	<p>If BLA or priority review NDA, send 60-day letter.</p>
<input type="checkbox"/>	<p>Send review issues/no review issues by day 74</p>
<input type="checkbox"/>	<p>Other</p>

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

Kelisha Turner
3/23/2009 02:31:33 PM
CSO

Margo Owens
3/24/2009 02:32:50 PM
CSO

NDA/BLA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

Application Information		
NDA # 22-483 BLA#	NDA Supplement #:S- N/A BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Tradename Established/Proper Name: (imiquimod) Dosage Form: Cream Strengths: 3.75%		
Applicant: Graceway Pharmaceuticals, LLC Agent for Applicant (if applicable): N/A		
Date of Application: December 19, 2008 Date of Receipt: December 19, 2008 Date clock started after UN: N/A		
PDUFA Goal Date: October 19, 2009	Action Goal Date (if different):	
Filing Date: February 17,2009 Date of Filing Meeting: January 30, 2009		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed Indication(s): AK face &/or scalp		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>Refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical disease Priority review voucher submitted
Resubmission after withdrawal? <input type="checkbox"/> Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR	

601.42)	
Collaborative Review Division (if OTC product): N/A	
List referenced IND Number(s): IND 30,432; IND 49,480; IND 49,464	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ora/compliance_ref/aiplist.html If yes, explain: If yes, has OC/DMPQ been notified of the submission? Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status Comments:	<input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
Exclusivity	

<p>Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</i></p> <p>If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES # years requested: 3 <input type="checkbox"/> NO
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<input checked="" type="checkbox"/> Not applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
<ol style="list-style-type: none"> 1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)). 3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? 	<input checked="" type="checkbox"/> Not applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>	
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<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <i>Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</i></p>		<input type="checkbox"/> YES <input type="checkbox"/> NO	
<p>If yes, please list below:</p>			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>			
Format and Content			
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p>Comments:</p>		<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input checked="" type="checkbox"/> Mixed (CTD/non-CTD)	
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>		<p>N/A</p>	
<p>If electronic submission: <u>paper</u> forms and certifications signed (non-CTD) or <u>electronic</u> forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3397), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p>Comments:</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
<p>If electronic submission, does it follow the eCTD guidance? (http://www.fda.gov/cder/guidance/7087rev.pdf)</p> <p>If not, explain (e.g., waiver granted): Waiver granted 4/8/08 via email. Hybrid.</p>		<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO	

<p>Form 356h: Is a signed form 356h included?</p> <p><i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Index: Does the submission contain an accurate comprehensive index?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Controlled substance/Product with abuse potential:</p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BLAs/BLA efficacy supplements only:</p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Patent Information (NDAs/NDA efficacy supplements only)	
<p>Patent information submitted on form FDA 3542a?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Debarment Certification	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, both the applicant and the U.S. Agent must</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>sign the certification.</p> <p><i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p> <p>Comments: Correction in 1-30-09 submission.</p>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Financial Disclosure	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Pediatrics	
<p><u>PREA</u></p>	
<p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	
<p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p>
<p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • <i>If no, request in 74-day letter.</i> • If yes, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) 	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p>Comments:</p>	

BPCA (NDAs/NDA efficacy supplements only):	
Is this submission a complete response to a pediatric Written Request? <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i> Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Prescription Labeling	
Check all types of labeling submitted. Comments:	<input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
Is electronic Content of Labeling submitted in SPL format? <i>If no, request in 74-day letter.</i> Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Package insert (PI) submitted in PLR format? If no , was a waiver or deferral requested before the application was received or in the submission? If before , what is the status of the request? <i>If no, request in 74-day letter.</i> Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
REMS consulted to OSE/DRISK? Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP? Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

OTC Labeling	
<p>Check all types of labeling submitted.</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Meeting Minutes/SPA Agreements	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments: IND 30,432 - 1/20/08; (b) (4)</p>	<input checked="" type="checkbox"/> YES Date(s): <input type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments: IND 49,480 - 10/29/08</p>	<input checked="" type="checkbox"/> YES Date(s): <input type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p>Comments: IND 49,480 - 3/30/01; Response to Request</p>	<input checked="" type="checkbox"/> YES Date(s): <input type="checkbox"/> NO

Turner, Kelisha C

From: Turner, Kelisha C
Sent: Thursday, March 19, 2009 5:00 PM
To: 'Sean Brennan'
Cc: Owens, Margo
Subject: FW: NDA 22-483, Tradename (imiquimod) Cream, 3.75% Clarification of CMC Request

Dr. Brennan,

Reference is made to your March 12, 2009 email request seeking further clarification of request 7 (page 2) for CMC information. Reference is also made to the filing communication dated March 2, 2009.

Clarification:

The reason for the request of rheograms and samples is that we would like to check if the proposed product meets CDER's current thinking about cream throughout the proposed shelf-life.

You have indicated in the NDA that the viscosity of the product declines substantially upon storage, and it approaches to the lower limit of the proposed viscosity acceptance criterion (b) (4) at the 6 month timepoint of 40C storage. Therefore, we want to examine 40C 6 month samples and corresponding rheograms. For comparison, we also want to examine 25C samples and their corresponding rheograms.

If you don't have 40C 6 month samples anymore, then please propose what samples with rheograms you can provide to assist CMC review of dosage form and viscosity acceptance criterion for NDA 22-483.

Kelisha C. Turner
Regulatory Health Project Manager
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration

Tel: 301-796-0766
Fax: 301-796-9894
kelisha.turner@fda.hhs.gov

From: Sean Brennan [mailto:sean.brennan@gracewaypharma.com]
Sent: Thursday, March 12, 2009 12:23 PM
To: Turner, Kelisha C
Subject: NDA 22-483 - Clarification of CMC Request

Dear Ms. Turner,

Thank you for returning my call. Reference is made to the request for additional information for NDA 22-483 dated March 2, 2009. Graceway is seeking further clarification of request 7 (page 2) for CMC information. The request states:

Submit 6 month 40°C samples (six units from each registration stability lot) to the NDA with rheograms (viscosity vs shear rate and shear stress versus shear rate) to assist with the assessment of dosage form. Submit 25°C stability samples (six units from each registration stability lot) with rheograms for comparison.

4/1/2009

In request 7, 6 month 40°C samples and 25°C samples are requested. Stability studies have progressed past the 6 month time at 40°C and samples (single use packets) are not available. We assume you are requesting "sample" rheograms from the respective storage conditions. Please clarify whether rheograms from the 6 month 40°C time point and rheograms from the 25°C or actual product samples stored at these conditions is being requested.

amples of product stored at the requested conditions are requested, please contact me to discuss what material is available to meet your request.

Please pass this request on to the reviewing chemist so that Graceway can get clarification and provide the most complete response.

Thank you.

Sincerely,

Sean Brennan PhD
VP, Regulatory Affairs
Graceway Pharmaceuticals LLC
340 Martin Luther King Jr. Blvd
Bristol, TN 37620

Office: 423-274-5210

Fax: 423-274-5610

Email: sean.brennan@gracewaypharma.com



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-483

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

Dear Dr. Brennan:

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

We also refer to your submission dated January 30, 2009.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 19, 2009.

During our filing review of your application, we identified the following potential review issues:

Clinical:

1. The effect of the product on cardiac repolarization has not been adequately addressed.

Pharmacology/Toxicology:

2. The quantity of the drug related impurity, most likely [REDACTED] ^{(b) (4)}, found during the stability studies was not identified.

CMC:

3. Drug product stability information is inadequate on related substances.
4. Quantitative information for the new impurity [REDACTED] ^{(b) (4)} in the clinical and toxicology test materials has not been provided.

Biostatistics:

5. Information regarding misrandomization is not adequately addressed as you have noted that several subjects in Studies 704 and 705 were misrandomized; however, only the information on the kit number actually allocated and associated treatment, not the kit number originally assigned are provided.
6. Information regarding the randomization problems experienced by Site 30 in Study 704 is not provided.

We also request that you submit the following information:

1. Data to address the potential of the product to affect cardiac repolarization.
2. Update drug product stability data for the four registration stability lots to include quantitative information of the following: new impurity [REDACTED] (b) (4) each specified identified degradant, each specified unidentified degradant, individual unspecified related substance, total unspecified related substances, and total related substances.
3. Provide quantitative information for the new impurity [REDACTED] (b) (4) in the clinical and toxicology test materials including the 5% imiquimod cream.
4. Submit the original treatment assignments (kit numbers) and associated treatment as generated by the IVRS for all subjects in Studies 702, 703, 704, and 705. You have noted that several subjects in Studies 704 and 705 were misrandomized; however, only the information on the kit number actually allocated and associated treatment, not the kit number originally assigned are provided in the listings of Appendix 16.1.7 of the respective study reports. The listings should permit the Agency to verify the misrandomizations described in the study reports. Provide information on the information that investigators provided to the IVRS and how the IVRS determined the appropriate kit numbers in Cycle 2 for subjects assigned to incorrect kits in Cycle 1. If possible, submit the randomization lists as SAS transport files.
5. Provide additional information regarding the randomization problems Site 30 in Study 704 experienced, including why the site was unable to receive randomization information from ClinPhone and how the study 'self-randomized' subjects.
6. Submit the following study report, and supporting materials, for Drug Metabolism Experiment No. R-837-DM-79 which contains information on the identification of metabolites for imiquimod which you refer to in your drug metabolism/identification subsection of your application.
7. Submit 6 month 40°C samples (six units from each registration stability lot) to the NDA with rheograms (viscosity versus shear rate and shear stress versus shear rate)

to assist with the assessment of dosage form. Submit 25°C stability samples (six units from each registration stability lot) with rheograms for comparison.

8. The only datasets that contain the randomized treatment codes are the derived analysis datasets (e.g. ad_ops and ad_opv). You should submit a ‘source dataset’ containing the randomization codes suitable for merging with the other ‘CRF source’ datasets in Studies 702, 703, 704, and 705.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

We are also reviewing the draft labeling submitted in Physician’s Labeling Rule (PLR) format, and have identified the following formatting issues:

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) (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>.

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.

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

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

Susan Walker

3/2/2009 12:53:36 PM

REQUEST FOR CONSULTATION

TO (Office/Division): **Division of Drug Marketing, Advertising and Communications**
Paul Loebach
WO 51, Room 3246

FROM (Name, Office/Division, and Phone Number of Requestor):
Kelisha Turner
Regulatory Project Manager
Division of Dermatology and Dental Products

DATE
January 27, 2009

IND NO.

NDA NO.
22-483

TYPE OF DOCUMENT
Original NDA

DATE OF DOCUMENT
December 19, 2008

NAME OF DRUG
Tradename (imiquimod)
Cream, 3.75%

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
5

DESIRED COMPLETION DATE
July 31, 2009

NAME OF FIRM: **Graceway Pharmaceuticals, LLC.**

REASON FOR REQUEST

I. GENERAL

- | | | |
|----------------------------------------------------------|--------------------------------------------------|------------------------------------------------------------|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|-------------------------------------------------|-------------------------------------------------|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--------------------------------------------------|------------------------------------------------------|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review the attached package insert, patient package insert, and carton and container labels.

PDUFA date: October 19, 2009

SIGNATURE OF REQUESTOR
Kelisha Turner, RPM

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

19 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/

Kelisha Turner

1/27/2009 01:33:23 PM



NDA 22-483

NDA ACKNOWLEDGMENT

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

Dear Dr. Brennan:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Imiquimod Cream, 3.75%

Date of Application: December 19, 2008

Date of Receipt: December 19, 2008

Our Reference Number: NDA 22-483

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 17, 2009 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatology and Dental Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

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

Sincerely,

{See appended electronic signature page}

Margo Owens
Team Leader, Project Management Staff
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Margo Owens

12/31/2008 01:16:47 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 49,480

Graceway Pharmaceuticals, LLC
Attention: Alicia M. Cabrelli
Sr. Manager, Regulatory Affairs
222 Valley Creek Boulevard
Suite 300
Exton, PA 19341

Dear Ms. Cabrelli:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for imiquimod cream, 3.75%.

We also refer to the meeting between representatives of your firm and the FDA on October 29, 2008. The purpose of the meeting was to discuss the content and format of the proposed marketing application for the imiquimod cream, 3.75% formulation utilizing the 2-week treatment cycle regimen for the treatment of actinic keratoses.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

{See appended electronic signature page}

Stanka Kukich, M.D.
Deputy Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 29, 2008
TIME: 10:30am-11:30am
LOCATION: WO Bldg. 22, Room 1311
APPLICATION: IND 49,480
DRUG NAME: imiquimod cream, 3.75%
TYPE OF MEETING: Pre-NDA

MEETING CHAIR: Stanka Kukich, M.D., Deputy Director

MEETING RECORDER: Barbara Gould, Chief, Project Management Staff

FDA ATTENDEES: (Title and Office/Division)

Stanka Kukich, M.D./Deputy Director, DDDP
Jill Lindstrom, M.D./Team Leader, Clinical, Dermatology, DDDP
Brenda Carr, M.D./Clinical Reviewer, DDDP
Mohamed Al-Osh, Ph.D./Team Leader, Biostatistics, DBIII
Constance Robinson-Kuiperi, RAC, PMP/Regulatory Information Specialist, DRRS
Sue Kang, B.S./Consumer Safety Officer, DDDP
Tapash Ghosh, Ph.D./Pharmacokinetics Reviewer, DCPIII
Barbara Hill, Ph.D./Pharmacology Reviewer, DDDP
Milena Lolic, M.D./Medical Officer, DDDP
Lydia Velazquez, Ph.D./Team Leader, Clinical Pharmacology, DPEIII
J. Paul Phillips, M.S./Regulatory Health Project Manager, DDDP
Paule Elie, MPH/Regulatory Health Project Manager, DDDP
Emelia Annum, M.S./Regulatory Health Project Manager, DDDP
Nichelle Rashid, B.S./Regulatory Health Project Manager, DDDP
Shulin Ding, Ph.D./Pharmaceutical Assessment Lead, ONDQA
Kathleen Fritsch, Ph.D./Biostatistian, DBIII
Barbara Gould, Chief, Project Management Staff, DDDP
Kelisha Turner, B.S./Regulatory Health Project Manager, DDDP

EXTERNAL CONSTITUENT ATTENDEES:

Jefferson Gregory, Chairman, CEO
John Bellamy, EVP and General Counsel
Mike Nordsiek, Executive Vice President, Product Development
James Lee, MD, Ph.D., Chief Medical Officer
Sharon Levy, MD, Vice President, Clinical Research
Jason Wu, MD, Senior Director, Clinical Research
James Kulp, Senior Director, Clinical Development
Sean Brennan Ph.D., Vice President, Regulatory Affairs

Alicia Cabrelli, Senior Manager, Regulatory Affairs
Robert Babilon, Senior Director, Product Development

(b) (4)

BACKGROUND:

Aldara[®] (imiquimod) Cream, 5% is currently approved under NDA 20-723 for the treatment of actinic keratoses (AK), superficial basal cell carcinoma (sBCC), and external genital warts (EGW). The treatment regimens for these indications are 2 times a week for 16 weeks, 5 times a week for 6 weeks, and 3 times a week for up to 16 weeks, respectively. Graceway Pharmaceuticals has developed a lower-strength formulation for AK with a dosing regimen that would be more convenient for patient use.

On July 27, 2007, Graceway met with the Agency to discuss the development plan for lower concentrations of imiquimod cream. In addition, Graceway met with the Agency on October 31, 2007 and on November 28, 2007 to specifically discuss the development program for the treatment of AK.

Purpose of Meeting:

This meeting is to discuss the content and format of the proposed marketing application for the imiquimod cream, 3.75% formulation utilizing the 2-week treatment cycle regimen for the treatment of actinic keratoses.

Regulatory

Question [1]:

Graceway proposes a new NDA for this submission. Does the Agency agree?

Response:

No. The proposed submission will be for a different strength of the active ingredient in a previously approved and marketed product. Such a change to an approved product by the applicant of the approved product would be submitted as a supplement.

Post Meeting Addendum:

Yes, the Agency agrees that Graceway could submit a new NDA. Normally, we would expect a change of the kind you propose to be submitted as a supplement. Different strengths or concentrations of one drug substance, active biological product, or combination product, if they are the same dosage form intended for the same route of administration and the same general indication(s), should be submitted in one original application if their qualitative composition is identical (drugs) or alike (biologicals).¹

¹ See FDA's Guidance for Industry – *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees* for details.

Question [2]:

Does that Agency agree to the proposed hybrid eCTD format? Does the Agency have any questions concerning the format of this submission?

Response:

We see that you were issued a waiver, please make sure you send your NDA application number to eSUB@fda.hhs.gov so our waiver database can be updated.

Question [3]:

Does the Agency agree to the proposed format for the eCTD table of contents? Does the Agency have any questions regarding the proposed table of contents?

Response:

The eCTD table of contents should follow FDA specifications. Please refer to the following web site and all applicable guidance and specifications including but not limited to the ones listed below.

The hybrid eCTD is a type of submission which can be very difficult for reviewers to navigate through the documents in the submission. Since you are submitting a hybrid eCTD, providing top level bookmarks to the applicable module TOC and overall TOC will be necessary from all pdf documents to avoid issues with navigation.

FDA eCTD website: <http://www.fda.gov/cder/regulatory/ersr/ectd.htm>

Final Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications. [PDF] (June 2008)

- [valid-values.xml \(1/30/2007\)](#) (includes U.S. specific values not in ICH version)
- [FDA eCTD Table of Contents Headings and Hierarchy](#) (updated 7/7/2005)
- [Study Data Specifications](#) (updated 8/7/2007)
- [Portable Document Format Specifications](#) (6/4/2008)
- [Transmission Specifications \[Word\] \[PDF\]](#) (updated 6/15/2005)
- [Specifications for eCTD Validation Criteria](#)

Question [4]:

Is the Agency willing to consider the merits of a unique brandname and label for this product?

Response:

Our current thinking remains that a single label is most appropriate; however, we would seek other consultation before making a final decision on this matter.

Meeting Discussion:

The sponsor reiterated their position to have a new tradename in order to reduce medication errors. The sponsor was advised to submit with the sNDA/NDA full justification for different tradename. However, a single label and same tradename would most likely reduce the rate of medication errors. The Agency will seek consultation from internal experts during the review period.

Chemistry, Manufacturing and Controls (CMC)

Question [1]:

Does the Agency agree that the Table of Contents for the CMC section is adequate?

Response:

No, we disagree. The drug substance section in Modules 2 and 3 needs to be expanded to include subheadings.

Question [2]:

The drug substance section of the CTD will cross-reference approved NDA 20-723 (Aldara Cream, 5% imiquimod). We propose the cross referencing be done by inclusion of a single-page document for the drug substance section that contains the statement: "Reference is made to the approved NDA 20,723 for Aldara Cream, 5% (imiquimod), for support for this section." Does the agency agree that this method of cross reference will be satisfactory?

Response:

No, one-page cross referencing will not be satisfactory. NDA 20-723 has been amended numerous times since its approval. For ease of review we recommend that an updated, complete CMC information package be provided for drug substance, and differences in CMC (if there are any) between the two NDAs should be clearly outlined.

Should you choose to reference the CMC information to NDA 20-723, you should provide summary information as well as clear reference to previously submitted information including dates, volume/section and page numbers. However, a complete, updated CMC information package is the Agency's recommendation.

Question [3]:

Graceway proposes to amend the NDA in mid-August with updated stability data to support the proposed expiry period for the product, considering that significant new data will be available prior to the end of the PDUFA review deadline. Does the agency agree with this proposed submission timeline?

Response:

We can not guarantee the review of the stability amendment during the course of the review cycle. We recommend that you submit all of the stability data that you plan to use to support the proposed NDA at the time of initial submission.

Question [4]:

Does the Agency agree that stability data from one lot of (b) (4), in addition to that submitted for the (b) (4) is sufficient to review for the approval of the (b) (4) t?

Response:

It is sufficient for filing but whether the NDA can be approved is a review issue. You will need to provide a strong justification to support your belief that data generated from (b) (4) fill size can be used to set specification and project expiry period for the (b) (4) fill size. Just stating that the two fill sizes share the same primary packaging component is inadequate. You will need to evaluate stress experienced by these two fill sizes during filling operation, and compare void space and surface to formulation ratio in the packets. In addition, please provide your plan to address seal integrity of (b) (4) packets.

Pharmacology/Toxicology

General Comments: It is acceptable for you to cross-reference the nonclinical studies contained in NDA 20-723 [Aldara (imiquimod) cream, 5%] to support the supplemental NDA submission for 3.75% imiquimod cream. However, you should provide a comprehensive summary of the nonclinical studies contained in NDA 20-723 in Module 2, Section 2.4 Nonclinical Overview of the eCTD supplemental NDA submission for the 3.75% imiquimod cream. This comprehensive summary should include a tabular presentation and written summary of all of the conducted nonclinical studies that you plan to rely on to support the safety of the 3.75% imiquimod cream. The tabular presentation should include a reference to the location of each nonclinical study in NDA 20-723 (i.e., date of submission, volume/section and page numbers).

Clinical Pharmacology

Question [1]:

Does the Agency agree that study GW01-0706 as conducted is adequate to support the submission of a 3.75% imiquimod formulation for the treatment of AK?

Response:

The study design synopsis as submitted seems to be adequate for a maximum usage study to support submission of the 3.75% imiquimod formulation for the treatment of AK. However, interpretation of the submitted study results is a review issue.

Meeting Discussion:

The sponsor agreed to present data from all PK studies for a side-by-side comparison with appropriate links and PK datasets.

Clinical/Biostatistics

Question [1]:

Graceway has conducted and will be submitting the results from four randomized placebo-controlled studies investigating two strengths and two regimens of a new imiquimod cream.

Does the Agency agree that there is adequate information for the filing and approval of an NDA for a 3.75% imiquimod cream product, used in a 2-week treatment cycle regimen?

Response:

Based on review of the briefing package, it appears that you have adequate information to file an NDA. However, the adequacy of the information to support approval is a review issue.

Question [2]:

Does the Agency agree that study GW01-0803, as designed, will provide adequate information regarding recurrence?

Response:

Yes.

Question [3]:

Does the FDA agree with this provision of narratives and case report forms within the clinical study reports?

Response:

Provide the rationale for the proposal to submit narratives for subjects who discontinued for an adverse event only if discontinuation is related to study drug. As is proposed for the case report forms, it is recommended that narratives be submitted for subjects who discontinued for any adverse event (whether assessed to be related or not to use of study drug).

Meeting Discussion:

The Agency stated that only sample case report forms should be included in the study report to avoid issues with CSR file size. All patient CRFs should be provided separate from the study report in a CRF folder by study and by site according to FDA guidance.

Sponsor agreed.

Question [4]:

Does the Agency agree with the plans for presentation and analysis of these efficacy and safety results, as described in the Clinical/Statistical section and Appendix 7 of this briefing package?

Response:

In general the plans for the presentation of the efficacy and safety results appear acceptable.

Keep in mind the following when assembling the application.

Submit electronic datasets in SAS transport form. The data sets should include demographic and baseline data as well as efficacy and safety data. Please note the following.

1. The database for the Phase 3 studies should include both raw variables (from the CRF) and derived variables suitable for conducting primary and secondary efficacy analyses.
2. Each data set should include the treatment assignments.

3. The submission should include adequate documentation for the data sets including definitions of each variable in the data set, formulas for derived variables and decodes for any factor variables so that all categories are well-defined in the documentation. The documentation should indicate which variables are derived.

In addition to the electronic data sets, the NDA submission should include the following items for the Phase 3 studies:

- a. Study protocols including the statistical analysis plan, protocol amendments with amendment dates, and an annotated copy of the Case Report Form.
- b. The generated treatment assignment lists and the actual treatment allocations (along with date of enrollment) from the trials.

Additional Statistical Comments:

1. The application package should provide a full discussion about how the efficacy and safety information from the studies was used to select your proposed dosing regimen, particularly with regard to the cross-study comparisons.
2. Studies 702 and 704 appear to have different overall success rates. The application should include a discussion of possible reasons for the difference and any implications of the differences.

Meeting Discussion:

The sponsor will submit analyses and explanation for the differences in efficacy outcomes in the Phase III trials and address the impact on dose selection.

The Agency raised the issue of multiplicity control for the secondary endpoints as outlined on page 23 of the briefing document. The sponsor agreed to address this issue in the sNDA/NDA submission.

Question [5]:

Does the Agency agree that it is acceptable to provide safety information from the Biopharmaceutics Study GW01-0706 within the ISS separate from that for the Phase 3 safety and efficacy studies?

Response:

Yes.

Question [6]:

Does the Agency agree that it is acceptable to provide cross-references directly to the detailed tables within the GW01-0706 Clinical Study Report, rather than to re-enter these tables within the ISS?

Response:

No. These tables should be re-entered within the ISS.

Question [7]:

Does the Agency agree that safety information collected from the marketed use of Aldara is not required to be included within the ISS?

Response:

The supplement should include summary information of the post-marketing experience with the active moiety, including major safety concerns (you should propose alternative locations to the ISS for this information).

Meeting Discussion:

The sponsor agreed to provide analysis by duration of adverse events in addition to frequency.

Question [8] (Previously Question 5 of Regulatory 8.4):

Does the Agency agree with this proposal for the 4-month Safety Update Report?

Response:

The proposal for the Safety Update is generally acceptable; however, the supplement should include updates on the postmarketing experience with the active moiety, including major safety concerns.

Question [9] (Previously Question 6 of Regulatory 8.4):

Does the Agency agree that study 1520-IMIQ, a study of the application of up to six 250 mg packets of Aldara for up to three 16-week cycles in 551 subjects, could be considered sufficient to meet the requirement for assessment of long-term safety of the 3.75% imiquimod cream formulation?

Response:

Provide data to support that the 3.75% has less systemic exposure than the 5% as used in study 1520-IMIQ. A determination of the need for a long-term safety study will be based on the adequacy of those data.

Question [10] (Previously Question 7 of Regulatory 8.4):

If the Agency agrees that the previously submitted 1520-IMIQ clinical study report is sufficient to meet the requirement for the assessment of long-term safety, does the Agency agree that no additional submission is required to support the 3.75% imiquimod cream application?

Response:

No. The study report should be submitted in the supplement.

Question [11] (Previously Question 8 of Regulatory 8.4):

Does the Agency agree that no additional data are needed to address the potential for QT/QTc interval prolongation?

Response:

See the response to question 9 (above) regarding systemic exposures of 3.75% versus 5%. Refer to the E14 guidance document.

Question [12] (Previously Question 9 of Regulatory 8.4):

Does the Agency have any additional comments or questions regarding this proposed marketing application?

Response:

The summaries of clinical efficacy and safety (summary documents) should be provided in Module 2. The integrated summaries of efficacy and safety (integrated analyses) should be provided in Module 5.

Additional Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND or NDA might identify additional comments or information requests.
2. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).
3. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.
4. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.
5. You are reminded that effective June 30, 2006 all submissions must include content and format of prescribing information for human drug and biologic products based on the new Physicians Labeling Rule (see attached website <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for additional details).

Linked Applications

Sponsor Name

Drug Name

IND 49480

GRACEWAY
PHARMACEUTICALS
LLC

IMIQUIMOD 5% TOPICAL CREAM

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/s/

STANKA KUKICH
11/26/2008



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 30,432

Graceway Pharmaceuticals, LLC
Attention: Alicia M. Cabrelli
Sr. Manager, Regulatory Affairs
222 Valley Creek Boulevard, Suite 300
Exton, PA 19341

Dear Ms. Cabrelli:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Imiquimod Cream, (b) (4) 3.75%.

We also refer to the meeting between representatives of your firm and the FDA on January 20, 2008. The purpose of the meeting was to discuss the development of new (b) (4) 3.75% strengths of imiquimod cream for the treatment of (b) (4).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Margo Owens, Regulatory Project Manager, at (301) 796-2110.

Sincerely,

{See appended electronic signature page}

Stanka Kukich, M.D.
Deputy Director
Division of Dermatology and Dental
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES



Meeting Date: January 20, 2008 **Time:** 3:00 P.M.
Location: WO Room 1315 **Meeting ID:** 23053
Topic: IND 30,432, imiquimod cream, (b) (4).75% for the
treatment of (b) (4)
Subject: End of Phase 2 meeting
Sponsor: Graceway Pharmaceuticals, LLC
Meeting Chair: Stanka Kukich, M.D./Deputy Division Director, DDDP
Meeting Recorder: Margo Owens/Regulatory Project Manager, DDDP

FDA Attendees:

Stanka Kukich, M.D./Deputy Division Director, DDDP
Jill Lindstrom, M.D./Team Leader, Clinical, DDDP
Brenda Carr, M.D./Clinical Reviewer, DDDP
Bogdan Kurtyka, CMC Reviewer, ONDQA
Lydia Velazquez, Pharm.D./Team Leader, Clinical Pharmacology, DPEIII
Tapash Ghosh, Ph.D./Clinical Pharmacology Reviewer, DPEIII
Mohamed Alesh, Ph.D./Team Leader, Biostatistics, DBIII
Clara Kim, Ph.D./Biostatistics Reviewer, DBIII
Margo Owens/Regulatory Project Manager, DDDP

Sponsor Attendees:

Graceway Pharmaceuticals, LLC

Michael Nordsiek, Executive Vice President, Product Development
Robert Babilon, Senior Director, Product Development
Sharon Levy, M.D., Vice President, Clinical Research
James Kulp, Senior Director, Clinical Research
Jason Wu, M.D., Senior Director, Clinical Research
James Lee, M.D., Chief Medical Officer
Sean Brennan, Vice President, Regulatory Affairs
(b) (4)

John Bellamy, Executive Vice President and General Counsel
Jefferson Gregory, CEO and Chairman

Purpose:

The sponsor requests input from the Agency on the development of a new dosing regimen for imiquimod cream for the treatment of (b) (4). The pre-meeting briefing document (submitted January 18, 2008) provides background and questions for discussion.

Administrative Comments:

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND might identify additional comments or information requests.
2. Please refer to the Guidance for Industry: Special Protocol Assessment and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT (SPA)**. Please clearly identify this submission as an SPA in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical or carcinogenicity) and include a reference to this End-of-Phase 2 meeting. Ten desk copies (or alternatively, an electronic copy) of this SPA should be submitted directly to the project manager.
3. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).
4. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens to contain and assessment of the safety and effectiveness of the

pediatric patients unless this requirement is waived or deferred.

5. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.
6. In response to a final rule published February 11, 1998, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this demographic analysis.
7. In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). Please plan to address this issue early in development.
8. We remind you that effective June 30, 2006, all submissions must include content and format of prescribing information for human drug and biologic products based on the new Physicians Labeling Rule (see attached website <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for additional details).
9. You are encouraged to request a Pre-NDA Meeting at the appropriate time.

Minutes Preparer: _____
Margo Owens/Regulatory Project Manager DDDP

Chair Concurrence: _____
Stanka Kukich, M.D./Deputy Division Director, DDDP

Linked Applications

Sponsor Name

Drug Name

IND 30432

GRACEWAY
PHARMACEUTICALS
LLC

ALDARA (IMIQUMOD) CREAM

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

/s/

STANKA KUKICH
02/29/2008

MEMORANDUM OF TELECONFERENCE

MEETING DATE: November 28, 2007
TIME: 2:30 P.M.
LOCATION: WO 22, Conference Room 5270
APPLICATION: IND 49,480
DRUG NAME: Imiquimod Cream (b) (4) 3.75%
TYPE OF MEETING: Teleconference – Follow-up to 10/31/07 Guidance Meeting

MEETING CHAIR: Jill Lindstrom, M.D./Lead Medical Officer

MEETING RECORDER: Margo Owens/Regulatory Project Manager

FDA ATTENDEES:

Susan J. Walker, M.D./Division Director, DDDP
Jill Lindstrom, M.D./Lead Medical Officer, DDDP
Brenda Carr, M.D./Clinical Reviewer, DDDP
Mohamed Al-Osh, Ph.D./Team Leader, Biostatistics, DBIII
Kathleen Fritsch, Ph.D./Biostatistian, DBIII
Margo Owens/Regulatory Project Manager, DDDP

EXTERNAL CONSTITUENT ATTENDEES:

John Bellamy/Executive Vice President
Jefferson Gregory/Executive Vice President
Michael Nordsiek/Executive Vice President, Product Development
(b) (4)

James Kulp/Senior Director – Clinical Research
Jason Wu, M.D./Senior Director – Clinical Research
Sharon Levy, M.D./Vice President – Clinical Research
Robert Babilon/Senior Director, Product Development
(b) (4)

James Lee, M.D./Chief Medical Officer
Sean Brennan/Regulatory

BACKGROUND:

On October 31, 2007, a Guidance meeting was held to discuss the sponsor's proposed development program for a lower strength and different dosing regimen for imiquimod cream, (b) (4) 3.75 mg. During that meeting, much of the discussion was devoted to challenges to the design of the study. As agreed during the October 31, 2007 meeting, this teleconference was held to continue the discussion on the study design issues. The pre-meeting briefing document (submitted November 16, 2007) provides background and questions for discussion.

Question #1

Does the Agency agree that guidance to physicians regarding product choice could be achieved via a differentiation of the patient populations, through protocol design, and ultimately through clear differentiation with the product label(s)?

Response

The Agency agrees that labeling that is an outcome of adequately-designed studies conducted in the appropriate patient populations may sufficiently inform clinicians in their treatment choices.

The sponsor should ensure that the populations proposed for study with the new formulations have disease of an extent to clearly warrant full face or scalp treatment. The draft protocols submitted in the briefing package for the October 31 guidance meeting, proposed enrollment of subjects with “5-20 clinically typical visible or palpable AKs within the treatment area.” This proposed target population may not adequately define candidates for full face or scalp treatment. For example, targeted therapy (e.g. liquid nitrogen) might be more appropriate for a subject with 5 lesions scattered over the face. Additionally, since the sponsor is proposing treatment of the full face or scalp, the proposed population should be sufficiently defined such that there is no overlap with the population for which imiquimod 5% is approved. For example, subjects with 5 to 8 lesions that are sufficiently close in proximity could represent a population who are candidates for treatment of a defined area for which the 5% product is approved (i.e. 25 cm²). The sponsor should ensure that the study population is sufficiently defined so as to be distinct from that for which the 5% product is indicated, such that labeling could describe the population for whom the new product and regimen would be intended. The sponsor agrees to the above recommendation and will incorporate them in the revised protocols.

The Agency also believes that safety and efficacy information of use of the product on the face versus the scalp would be useful for practitioners.

Question #2

Does the Agency have any additional comments or suggestions on our plans to assess dose/regimen selection directly within the Phase 3 pivotal studies?

Response

The Agency continues to believe that a sequential approach of conducting a Phase 2 study prior to conducting Phase 3 studies would be most informative. However another alternative to consider might be to conduct one Phase 3 study with all four treatment arms and use this information to design a smaller second study with a reduced number of arms. This proposal would still allow within-trial comparisons of all regimens but would permit a smaller second study. If time is a factor, the sponsor could consider selecting the design for the second study at an interim analysis. For interim analyses the protocol should include a plan to ensure blinding (e.g. through DSMC).

Under the sponsor's proposal to evaluate the different cycle regimens in different studies, it should be noted that the consistency of study findings for a dosing regimen might be impacted by study-to-study variability, which might impact the selection of one dose based on the efficacy and safety considerations.

Question #3

We would appreciate your input on the study designs in order to ensure that the data collected are acceptable for review in the NDA submission. Does the Agency have any additional comments on the design of the Phase 3 studies as proposed?

Response

For the primary analysis of the complete clearance rate, the sponsor has proposed using logistic regression with terms for treatment, center, treatment area location, and baseline AK count. The sponsor should clarify whether the baseline AK count covariate is for the stratification factor (5-13 or 14-20) or the actual count. This model includes a fairly large number of terms for a relatively small study of about 60 (or 80) subjects per treatment arm and the number of subjects within each group will likely be small. Such a model may not be justified based on the proposed sample size. The sponsor may need to consider reducing the number of terms in the model. It is not clear from the submission whether a threshold of 13 lesions for stratification would allow for adequate numbers of subjects in each grouping.

The sponsor stated that they plan to modify the analysis to a CMH (Cochran-Mantel-Haenszel) test stratified on site. The Agency noted from the previous submission for the meeting held on October 31, 2007, that the sponsor plans to randomize with stratification on lesion count and if so, the analyses should account for stratification factors. The sponsor responded that they plan to remove the stratification on lesion count from the randomization.

In addition, the utility of testing the relative efficacy of the (b) (4) 3.75% formulations if one formulation is superior to vehicle is not clear as the study objective is to compare each concentration with vehicle. Dose/regimen selection will need to be based on both efficacy and safety considerations.

As previously conveyed, the Agency recommends listing the criteria for excluding subjects from the per protocol population in the protocol. The sponsor is encouraged to limit the number of secondary endpoints to a small set of clinically relevant endpoints and incorporate multiplicity control on the set of secondary endpoints.

Also, please see the response to Question #1.

The Agency advised that the sponsor consider the lesion thickness in their development program.

Question #4

Does the Agency agree that dermal safety studies are not required for development of the lower-strength imiquimod cream formulations?

Response

Yes this is acceptable, since the new products are identical to the 5% product except for (b) (4)

Minutes Preparer: _____
Margo Owens/Regulatory Project Manager, DDDP

Chair Concurrence: _____
Jill Lindstrom, M.D./Lead Medical Officer, DDDP

Linked Applications

Sponsor Name

Drug Name

IND 49480

GRACEWAY
PHARMACEUTICALS
LLC

IMIQUIMOD 5% TOPICAL CREAM

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

/s/

JILL A LINDSTROM
12/11/2007



IND 49,480

Graceway Pharmaceuticals, LLC
Attention: Alicia M. Cabrelli
Senior Manager, Regulatory Affairs
222 Valley Creek Boulevard, Suite 300
Exton, PA 19341

Dear Ms. Cabrelli:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Imiquimod Cream.

We also refer to the meeting between representatives of your firm and the FDA on October 31, 2007. The purpose of the meeting was to obtain the Agency's input on the development program for a lower strength and different dosing regimen of imiquimod cream, (b) (4) 3.75 mg for the treatment of actinic keratoses.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Margo Owens, Regulatory Project Manager, at (301) 796-2110.

Sincerely,

{See appended electronic signature page}

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

MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 31, 2007
TIME: 9:00 A.M.
LOCATION: WO 22, Conference Room 1315
APPLICATION: IND 49,480
DRUG NAME: Imiquimod Cream, (b) (4) 3.75%
TYPE OF MEETING: Guidance Meeting

MEETING CHAIR: Susan J. Walker, M.D./Division Director

MEETING RECORDER: Margo Owens/Regulatory Project Manager

FDA ATTENDEES:

Susan J. Walker, M.D./Division Director, DDDP
Jill Lindstrom, M.D./Team Leader, Clinical, DDDP
Brenda Carr, M.D./Clinical Reviewer, DDDP
Bogdan Kurtyka/Chemistry Reviewer, ONDQA
Mohamed Al-Osh, Ph.D./Team Leader, Biostatistics, DBIII
Kathleen Fritsch, Ph.D./Biostatistcian, DBIII
Abimbola Adebowle, Ph.D./Pharmacokinetics Reviewer, DPEIII
Margo Owens/Regulatory Project Manager, DDDP

EXTERNAL CONSTITUENT ATTENDEES:

John Bellamy/Executive Vice President
Jefferson Gregory/Executive Vice President
Michael Nordsiek/Executive Vice President, Product Development
(b) (4)

James Kulp/Senior Director – Clinical Research
Jason Wu, M.D./Senior Director – Clinical Research
Sharon Levy, M.D./Vice President – Clinical Research
Robert Babilon/Senior Director, Product Development
(b) (4)

James Lee, M.D./Chief Medical Officer
Sean Brennan/Regulatory

PURPOSE:

To provide guidance on the development program for a lower strength and different dosing regimen of imiquimod cream, (b) (4) 3.75 mg for the treatment of actinic keratoses. The pre-meeting briefing document (submitted September 26, 2007) provides background and questions pg. 8) for discussion.

Chemistry, Manufacturing and Controls:

Question 8:

Does the Agency agree that these responses adequately address the questions posed in the July 27, 2007 meeting regarding the origin of isostearic acid, polysorbate 60, and sorbitan monostearate, as well as the testing for ethylene oxide and dioxane impurities of polysorbate 60?

Response:

Yes, we agree.

Pharmacology/Toxicology:

There are no pharmacology/toxicology questions identified in this briefing package.

Clinical Pharmacology/Biopharmaceutics:

We acknowledge the sponsor's revised PK maximal use study synopsis for the 3.75 % imiquimod formulation in patients with Actinic Keratoses (AK), based on the comments provided at the guidance meeting held with the Agency on July 27th, 2007. The comment referred to was the one that stated that the PK study should be conducted with the to-be-marketed formulation under maximal use conditions (e.g. diseased patients with a severity towards the upper end of the proposed indication, maximal dosing regimen and total body surface area) that is consistent with your proposed Phase 3 clinical trials. We have the following comments with regards to the revised PK study design:

1. The proposed revised PK study designed to be conducted under maximal use conditions appears reasonable in terms of the entry criteria for testing under maximal use conditions (i.e. at least 10 clinically typical visible or palpable AK lesions within the treatment area (balding scalp or face)).
 - Please clarify why the expected number of subjects that would provide steady-state PK data would be 12 out of approximately 20 enrolled subjects.
 - Please clarify how the information obtained from instructing patients to apply the cream to an alternate site of approximately 200 cm² area (e.g., arms) if they experience any sign or symptom in the treatment area, would be used in the context of maximal use conditions that is consistent with the proposed clinical trials.

2. The results of a maximal use pharmacokinetic study conducted with the 3.75 % imiquimod formulation in patients with AK may support the submission of the (b) (4) formulation in patients with AK provided that the following conditions are met:
 - They are both in the same dosage form, and proportionally similar in their active and inactive ingredients. This may be addressed by providing a comparison of the quantitative and qualitative composition of both the (b) (4) and 3.75 % formulations and highlighting the differences between both formulations.
 - The total involved body surface area, the dosing regimen and the treatment duration are no greater than that studied with the 3.75 % formulation.
 - The systemically related adverse events obtained with the (b) (4) formulation are comparable or less than that obtained with the 3.75 % formulation. This may be

addressed by submitting a comparison of the adverse event profiles for the (b) (4) and 3.75 % imiquimod formulations for the different dosing regimens that will be proposed with special emphasis on the systemically related adverse events.

3. Please see responses to questions 1 and 2 above.

Clinical/Biostatistics:

Introductory Statement

The sponsor states the following on p.2 of the briefing package: "The rationale to proceed to Phase 3 studies with several doses and regimens was discussed during the July 27, 2007 meeting, and, with Agency concurrence, Graceway has accepted the risk of proceeding directly to the Phase 3 studies." At the guidance meeting held on July 27, 2007, the Agency strongly recommended that the sponsor conduct Phase 2 dose-ranging studies prior to proceeding to Phase 3, and the Agency stands by those recommendations. The sponsor is referred to the minutes of the guidance meeting held on July 27, 2007. The Agency did not (and does not) "concur" with the sponsor's plans to proceed to Phase 3; we acknowledge that the sponsor has accepted the risk of so doing.

Question 4: Does the Agency agree that the proposed clinical program as described will support a marketing application for a lower strength imiquimod cream ((b) (4) 3.75%) in the treatment of actinic keratoses of the face or balding scalp?

Response: The sponsor proposes to conduct seven clinical studies to support a marketing application:

- a pharmacokinetic study under conditions of maximal use
- a study in which the approved dosing regimen for Aldara would be compared to the proposed new formulations and dosing regimens (the sponsor intends that this trial would be "supportive" and conducted in parallel with the Phase 3 trials)
- four randomized, double-blind, placebo-controlled Phase 3 studies identical in design except for duration of treatment and interval cycles
- a Phase 4 observational recurrence study in subjects who completely clear in Phase 3

The development program, as presented, may not be adequate to support a marketing application for reasons which include:

1. The development program does not address dermal safety studies; however, this issue will be taken under further consideration (following internal agency discussion on how the new formulations compare to the currently-marketed 5% formulation)
2. AK is a chronic indication, and the long-term safety should be addressed. The sponsor may be able to incorporate the assessment of long-term safety into the recurrence study. Alternatively, information from previously-conducted studies may fulfill long-term safety data needs outlined in the ICH E1A Guideline.

Drug development is a sequential process where findings from early studies are used to appropriately design later studies. The following comments are provided in the context of the Agency's recommendation that the sponsor conduct Phase 2 dose-ranging studies before proceeding to Phase 3 studies:

1. The Agency does not consider that the proposed study GW01-0701 (0701) would adequately address the recommendations for dose-ranging studies, the elements of which

are frequency, concentration and duration of treatment. Additionally, the study will be conducted in parallel with the Phase 3 trials, and the regimens to be studied are identical to those proposed for study in Phase 3. The agency continues to strongly recommend that the sponsor conduct Phase 2 dose-ranging studies; please see the minutes of the July 27, 2007 guidance meeting. The Agency strongly recommends conducting the dose-ranging study (b) (4) prior to conducting the Phase 3 studies. The final design of the confirmatory studies should be based on the information learned in the dose-ranging study. Phase 2 studies provide important estimates for powering Phase 3 studies. Currently, the sponsor has not provided any information to support that the Phase 3 studies are adequately powered. Collecting information on the vehicle response during Phase 2 would also assist in adequately powering the Phase 3 studies. In addition, the sponsor may be able to eliminate some of the dosing regimens based on the results of the study and therefore greatly reduce the scope and complexity of the Phase 3 studies. If multiple dosing regimens are carried into Phase 3, the Agency recommends comparing all dosing regimens within the same studies, rather than conducting separate studies for separate regimens.

2. The extent to which study (b) (4) would provide comparative risk/benefit data for the new formulations versus Aldara may be limited given that treatment will be limited to 25 cm² and the sponsor proposes treatment of either the entire face or balding scalp with the new formulations. This study also may not adequately address the relative risk and benefit of the proposed treatment regimens when applied to the entire face or balding scalp. Further, dosing will be limited to one packet of study product per application, while the sponsor proposes dosing of up to two packets of the new formulations per treatment. For the new formulations, usage instructions should be specific so as to guide subjects as to when two packets of product might be needed as opposed to one.

Meeting Discussion:

Much of the meeting was devoted to discussion of challenges to design of the study in which the approved dosing regimen for Aldara would be compared to the proposed new formulations and dosing regimens. The agency acknowledged the challenges to design of the study and recommended a follow-up meeting (or teleconference) for continued discussion of the issues. The sponsor was advised to submit specific questions prior to the follow-up meeting for discussion at the meeting.

Addendum: A teleconference to discuss study design was scheduled and held on November 28, 2007 (meeting minutes to follow).

3. We acknowledge the sponsor's declaration that, "one formulation (b) (4) 3.75%) at one dose regimen (either 2-week cycles (b) (4)) will be submitted in an NDA" (p. 11 of briefing). It is recommended that that concentration and dosing regimen be identified in Phase 2. The sponsor will need to adequately demonstrate how the selected new formulation and dosing regimen compare to the 5% in the treatment of AK, and undertaking the comparison in Phase 3 would allow for one label for both formulations and dosing regimens. However, the sponsor will need to adequately justify the need in the marketplace for both formulations and dosing regimens. The efficacy signal with the new formulation/regimen must be robust. Information on how the new and currently-

marketed concentrations and dosing regimens compare is important so that clinicians have a scientific basis for their treatment recommendations.

Question 5: Does the Agency agree with the proposed study design, as described in the complete protocols, support a marketing application for AK?

Response: Safety assessments in study (b) (4) should also include interval laboratory evaluations. The Agency recommends completing the dose-ranging study before finalizing the designs of the confirmatory studies to incorporate the findings from the dose-ranging study.

Question 6: Does the Agency agree with the proposed efficacy and safety endpoints and the statistical methods as described to determine safety and efficacy of the investigational formulations?

Response: No. Although it is premature to comment on the protocols for the confirmatory studies, the Agency has the following preliminary comments:

- The recommended primary endpoint is 100% clearance of AK at efficacy assessment.
- Proposed procedures for safety monitoring may be a function of what is already known about a class of products. However, proposed procedures for safety monitoring may more specifically be a function of what is learned about a particular product in its sequential development, e.g. Phase 2 dose-ranging. These are among the factors that may ultimately inform the safety monitoring proposed for Phase 3.
- The Agency does not agree with the proposal to conduct 5 simultaneous studies and therefore cannot provide concurrence on the proposed statistical analysis plans. However, the following comments on statistical methods can be generally applied to Phase 3 studies regardless of the overall design:
 - a. The protocol should adequately define the ITT and per protocol populations (including the criteria for excluding subjects from the per protocol population), as well as specify primary and sensitivity analysis methods for addressing the handling of missing data to ensure that the conclusions are not driven by the method of imputation.
 - b. The sponsor is encouraged to limit the number of secondary endpoints to a small set of clinically relevant endpoints and address the issue of multiplicity on the set of secondary endpoints.

Question 7: Does the Agency have any additional comments regarding the described clinical plan for the development of a low strength imiquimod cream for the treatment of AK?

Response: The agency has no additional comments at this time.

Additional Administrative Comments:

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND might identify additional comments or information requests.

2. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).
3. We remind you of the Pediatric Research Equity Act of 2003 which requires all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain and assessment of the safety and effectiveness of the pediatric patients unless this requirement is waived or deferred.
4. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.
5. In response to a final rule published February 11, 1998, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this demographic analysis.
6. In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). Please plan to address this issue early in development.
7. We remind you that effective June 30, 2006, all submissions must include content and format of prescribing information for human drug and biologic products based on the new Physicians Labeling Rule (see attached website <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for additional details).

ACTION ITEMS:

1. The Agency will schedule a teleconference with the sponsor to discuss study design.
2. The sponsor will submit questions for the follow-up teleconference.

Minutes Preparer: _____
Margo Owens/Regulatory Project Manager, DDDP

Chair Concurrence: _____
Susan J. Walker, M.D./Division Director, DDDP

Linked Applications

Sponsor Name

Drug Name

IND 49480

GRACEWAY
PHARMACEUTICALS
LLC

IMIQUIMOD 5% TOPICAL CREAM

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

/s/

STANKA KUKICH

11/30/2007

signing for Dr. Susan Walker, Division Director



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 30,432

Graceway Pharmaceutical, LLC
Attention: Sean Brennan, Ph.D.
Vice President, Regulatory Affairs
340 Martin Luther King Jr. Blvd., Suite 300
Bristol TN 37620

Dear Dr. Brennan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for imiquimod for the treatment of actinic keratosis (b) (4)

We also refer to the meeting between representatives of your firm and the FDA on July 27, 2007. The purpose of the meeting was to provide general guidance for development of new strength of imiquimod cream for the Investigational New Drug Application (IND) under 21 CFR 312.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Vickey Lutwak, Regulatory Project Manager, at (301) 697-2445.

Sincerely,

{See appended electronic signature page}

Stanka Kukich, M.D.
Deputy Director
Division of Dermatology Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 27, 2007
TIME: 9:00 AM EST
LOCATION: WO 22 Room 1313
APPLICATION: IND 30,432
DRUG NAME: Imiquimod
TYPE OF MEETING: Guidance Meeting
MEETING CHAIR: Stanka Kukich, M.D./Deputy Division Director, Division of Dermatology and Dental Products (DDDP), HFD-540
MEETING RECORDER: Vickey Lutwak Regulatory Project Manager, DDDP, HFD-540

FDA ATTENDEES:

Stanka Kukich, M.D./Deputy Division Director, DDDP, HFD-540
Brenda Carr, M.D./Clinical Reviewer, DDDP, HFD-540
Kathleen Fritsch, Ph.D./Reviewer, Division of Biometrics III, HFD-725
Paul Brown, Ph.D./Supervisory Pharmacologist, DDDP, HFD-540
Abimbola Adebowale, Ph.D./Pharmacokinetics Reviewer, DCPIII, HFD-880
Tamika White/Regulatory Project Manager, DDDP, HFD-540
Vickey Lutwak/Regulatory Project Manager, DDDP, HFD-540

EXTERNAL CONSTITUENT ATTENDEES:

Graceway Pharmaceuticals:

Michael Nordsiek/ Executive Vice President, Product Development
Robert Babilon/Senior Director, Product Development
Sharon Levy, M.D./Vice President, Clinical Research
James Kulp/Senior Director, Clinical Research
Jason Wu, M.D./Senior Director, Clinical Research
James Lee, M.D./Chief Medical Officer

(b) (4)

Sean Brennan/Vice President, Regulatory Affairs

(b) (4)

Jefferson Gregory/CEO, Graceway Pharmaceuticals

MEETING OBJECTIVES:

Purpose of the Meeting: To provide general guidance for development of new strength of imiquimod cream for the treatment of actinic keratosis (b) (4)

(b) (4) for Investigational New Drug Application (IND) 30,432 under 21 CFR 312.

Chemistry, Manufacturing and Controls (CMC):

Question 24

Does the Agency agree that the CMC information can be provided to one IND (e.g. 30,432) that would be cross-referenced by the remaining INDs?

FDA Response:

Yes, we agree.

Additional Comments:

1. Please confirm the origin of following excipients used in new formulations: isostearic acid, polysorbate 60, and sorbitan monostearate.

Pharmacology/Toxicology:

Question 22

Does the Agency agree that no additional nonclinical studies are required to support the conduct of the clinical studies as described in the briefing package?

FDA Response:

Yes.

2. Two toxic impurities, (b) (4) are not covered in the NF monograph of polysorbate 60. Please address this issue.

Question 23

Does the Agency agree that no additional nonclinical studies are required to support the submission of an NDA for the (b) (4) 3.75% imiquimod creams?

FDA Response:

Yes.

Clinical Pharmacology/Biopharmaceutics

Question 2

Does the Agency agree that a pharmacokinetic study of the 3.75% formulation in patients with AK, conducted in parallel with the Phase 3 efficacy studies, is adequate to support the requirements for marketing applications for the (b) (4) 3.75% imiquimod creams in AK, (b) (4) patients?

FDA Response:

The results of the proposed pharmacokinetic study of 3.75 % imiquimod cream in patients with actinic keratoses (AK) may not be adequate to support the requirements of marketing applications for the 3.75 % creams in patients with (b) (4) due to differences in the disease states, dosing regimens and site of application proposed for each disease state.

We acknowledge the synopsis of the proposed maximal use PK study to be conducted with the 3.75% cream in patients with AK provided in this briefing package. We note that the patients proposed for the PK study are at the lower end of disease severity with the shorter treatment duration (i.e. 2 week treatment cycle (b) (4)) of that proposed for the Phase 3 clinical trial. Please note that the PK study should be conducted with the to-be-marketed formulation under maximal use conditions (e.g. diseased patients with a severity towards the upper end of the proposed indication, maximal dosing regimen and total involved body surface area) that is consistent with your proposed Phase 3 clinical trials.

We recommend that the sponsor conduct the PK studies in patients with AK (b) (4) using the to-be-marketed formulation under maximal use conditions. (b) (4)

Generally, it is preferable to conduct the PK studies prior to conducting the Phase 3 clinical trials because the results may provide information that will guide the design of the Phase 3 studies.

Meeting Discussion:

PK estimates obtained at steady state are acceptable provided that the achievement of steady state is confirmed and provided in your report.

Clinical and Biostatistics:

1. (DS). Does the Agency agree that no dermal safety studies in volunteers are required to be included in a marketing application(s) for the (b) (4) 3.75% imiquimod creams?

FDA Response: The presence of the toxic impurities may necessitate the conduct of dermal safety studies. The sponsor is requested to address this issue.

Overall Clinical Program (OCP)

3. (OCP) Does the Agency agree that a placebo that closely matches the 3.75% imiquimod cream formulation is appropriate for use in clinical studies of (b) (4) 3.75% imiquimod creams?

FDA Response: The sponsor should ensure that a placebo is sufficiently similar to any active so as to protect the blind. Should the blind be compromised because of obvious differences in appearances between the active and the placebo, other measures should be instituted to maintain the blind, e.g. implement measures in the conduct of the study.

4. (OCP) Does the Agency agree that each of the proposed clinical programs is adequate, from a clinical safety perspective, to independently support a marketing application for each patient population?

FDA Response: Proposed procedures for safety monitoring may be a function of what is already known about a class of products. Additionally, proposed procedures for safety monitoring may more specifically be a function of what is learned about a particular product in its sequential development, e.g. Phase 2 dose-ranging. These are among the factors that may ultimately inform the safety monitoring proposed for Phase 3.

Although this question focuses on safety, the Agency also has the following comments on the overall development strategy that applies to each indication. The Agency recommends conducting additional Phase 2 dose-ranging studies before proceeding to Phase 3. The sponsor has not provided adequate justification that the proposed new dosing regimens will strike the best balance for safety, efficacy, and compliance. Evaluating a variety of regimens (concentration, frequency, duration) within the same study will provide useful information to select a regimen with an acceptable efficacy and safety profile to use in confirmatory studies. The dose-ranging studies should also include an arm at the approved dose (b) (4) to provide information on the tradeoffs in safety and/or efficacy with the alternate dosing regimens. By carefully evaluating various regimens in Phase 2, the number of arms in the Phase 3 studies can be reduced. Estimates from Phase 2 studies can be used to more accurately estimate Phase 3 sample sizes. If after conducting dose ranging studies you ultimately elect to include multiple dosing regimens in Phase 3, the regimens should all be evaluated within the same study rather than in separate studies so that the benefits and risks of different regimens can be directly compared.

See also the responses to Questions 5, 11, and 17 for indication-specific recommendations about dose-ranging.





Actinic Keratoses (AK)

11. (AK) Does the Agency agree that each of the proposed clinical programs as described will support an indication for treatment of actinic keratoses of the face?

FDA Response: No. Please see the responses to Questions 4 and 5 regarding the need for Phase 2 dose-ranging studies. If you ultimately elect to follow multiple dosing regimens to Phase 3 (such as 2 week and 3 week treatment periods) these should be evaluated within the same study rather than in separate studies so that the benefits and risks of different regimens can be directly compared.

Meeting Discussion:

The sponsor was advised to submit a package which includes a discussion of the difficulties of designing a trial in which the new and currently-marketed products are compared. The package should also provide the sponsor's rationale for believing that they can rely on existing data for comparative purposes.

The sponsor was advised that they could obtain comparative data to the 5% concentration in Phase 2 or 3, but they would need to ensure that the comparative data were adequate to allow for benefit/risk assessment.

12. (AK) Does the Agency agree with the design of and rationale for the proposed regimens, including daily dosing, provision for rest periods and designation of two cycles as the treatment regimen?

FDA Response: Please see the responses to Questions 4 and 5 regarding dose-ranging studies.

13. (AK) Does the Agency agree with the proposed study population including the described AK and treatment area characteristics?

FDA Response: The proposed population may be appropriate.

14. (AK) Does the Agency agree with the proposed efficacy and safety endpoints and the statistical methods to determine safety and efficacy of the study formulations?

FDA Response: The primary endpoint should be the proportion of subjects with complete clearance of all AK (baseline and new) at efficacy assessment. Logistic regression may be acceptable for analyzing complete clearance. Additional comments on the statistical analyses will be provided after complete protocols have been submitted

15. (AK) Does the Agency agree that treatment efficacy may be assessed at the end of study visit (b) (4) without additional follow-up to assess recurrence?

FDA Response: No. The development program should provide for the assessment of recurrence.

Meeting Discussion:

Recurrence data are required, and submission in Phase 4 is acceptable.

16. (AK). Does the Agency have any additional comments regarding the described clinical plan for the development of (b) (4) 3.75% imiquimod creams for the treatment of AK?

FDA Response: The sponsor should attend an End-of-Phase 2 meeting at the appropriate time.

(b) (4)



Regulatory (REG)

25. (REG) Does the Agency agree that the clinical program as described can be conducted under the current INDs for the relevant indications, updated as necessary with relevant CMC and Clinical information?

FDA Response: Yes. The development programs for the new products can be conducted under the current INDs.

26. (REG) Does the Agency agree that a full pediatric waiver for low dose imiquimod cream is reasonable?

FDA Response: (b) (4)
(b) (4) A full waiver may be acceptable for the AK (b) (4)
(b) (4) A formal request with rationale should be provided in the marketing application for the pediatric age groups for which the sponsor requests a waiver.

Meeting Discussion:

(b) (4)

27. (REG) Does the Agency agree that NDA(s) based upon the results of clinical trials with (b) (4) the 3.75% imiquimod cream(s) would be submitted with a package insert separate from that of Aldara?

FDA Response: For one product, the Agency recommends one package insert and one NDC number. The sponsor is requested to provide the rationale for considering separate NDAs for each indication.

Meeting Discussion:

The Division's current thinking is that under the Physicians Labeling Rule (PLR), it is most appropriate to have all concentrations of a product consolidated into one package inserts. However, this may change, and this issue will be further considered during the review process.

Administrative Comments:

1. Comments shared today with the sponsor are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of the information submitted to the IND might identify additional comments or information requests.
2. The sponsor is encouraged to request and attend an End-of-Phase 2 meeting to obtain regulatory agreements for clinical endpoints and study design for Phase 3

trials. Comments on phase 1 and 2 trials do not necessarily constitute commitments that can be extrapolated to Phase 3 trials.

3. The sponsor is reminded of the Pediatric Research Equity Act of 2003 which requires all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain and assessment of the safety and effectiveness of the pediatric patients unless this requirement is waived or deferred. Please request the appropriate action.

ATTACHMENTS/HANDOUTS:

E-mail attachment from Graceway (7/26/07) with their list of issues to be discussed and those needing no additional discussion.

FDA Responses which do not require additional discussion:

Question 24 (CMC)

(line 53): The information concerning the origin of certain excipients will be provided at a future date.

(line 56): The information concerning (b) (4) will be provided at a future date.

Question 22 (Nonclin) (line 61): Agree that no additional nonclinical studies are required to support clinical studies.

Question 23 (Nonclin) (line 69): Agree that no additional nonclinical studies are required to support an NDA submission.

Question 1 (DS) (Line 117): Sponsor will address the issue of the relationship of potential toxic impurities and dermal safety studies following the meeting.

Question 3 (OCP) (line 120): No further discussion required regarding the acceptability of placebo.

Question 4 (OCP) (line 127): Sponsor request that the issue of Phase 2 studies should be discussed within each specific indication.

(b) (4)

Question 12 (AK) (line 248): No further clarification required regarding this specific question on the design of the treatment regimens; this issue is addressed in questions 4 and 5.

Question 13 (AK) (line 254): No further clarification required regarding the proposed population.

Question 14 (AK) (line 259): No further clarification required regarding the proposed efficacy and safety endpoints and the statistical methods.

Question 16 (AK) (line 272): No further clarification required regarding the FDA recommendation for an End of Phase 2 Meeting.

(b) (4)

Question 25 (REG) (line 341): No further questions regarding the submission of CMC information to INDs.

FDA Responses which we would like to discuss:

Regulatory

Question 27 (REG) Line 360: The Agency states that one package insert is recommended for one product with one NDC number. Would the potential formulations of (b) (4) 3.75% imiquimod cream be considered as separate products, and separate from the 5% imiquimod cream? We note that the recently approved Differin (0.3% adapalene) is presented in a package insert separate from the 0.1% adapalene product.

Actinic Keratoses

Question 11 (AK)

(line 227) Please note that the sponsor intends to submit a single concentration in a single regimen for NDA review for treatment of AK.

Noting the recommendation for Phase 2 studies, the sponsor would like to discuss the rationale for proceeding to the Phase 3 studies as a manner to identify the one regimen for submission in an NDA, as described in the briefing package.

(Line 244):

Does the word “need” mean that the 5% product must be included in submitted studies, as a mandatory requirement?

If so, does the 5% product need to be a) included in Phase 2, or included in Phase 3? If included, is the regimen to be included the currently approved (2 times a week for 16 weeks) or the investigational (2 or 3-week treatment cycles) regimen?

Is the general recommendation for Phase 2 studies in AK a mandatory requirement or may the sponsor acknowledge that there is a level of risk to proceed directly into Phase 3?

Does the use of the word “should” indicate that there is a mandatory requirement, or a recommendation, for the inclusion of a 5% arm in dose ranging studies for AK?

Question 15 (AK) (line 270): Sponsor notes that the current label does not include recurrence data for AK. We do propose that, if required, this data could be collected following completion of the Phase 3 studies and submitted as a post-approval commitment.

(b) (4)

Clinical Pharmacology

Question 2 (Clin Pharm)

(line 95) For AK, the efficacy studies are proposed to have two treatment cycles of two or three weeks; would a PK study with one three-week treatment cycle be sufficient to support both treatment regimens?

(line 95) The intended treatment regimen of 3 weeks of daily use may not be tolerated by all patients enrolled in a PK study; Sponsor requests that patients partially completing a PK study would be included in the analysis of the PK profile.

(line 97): Since the 3.75% formulation will be the maximum dose studied, our intent is to study this strength. (b) (4)

(line 98): Concerning disease severity in AK, a Phase 3 protocol may specify a range of 5-15 lesions; would his range be acceptable as an inclusion criteria for a PK study?

(line 102) Current PK estimates are that steady state may be reached in 2 weeks. (b) (4)

(line 107): Sponsor believes that systemic levels are not predictive of efficacy, that total exposure will be within the range of previously used regimens, and that it would be reasonable to conduct PK studies (using the to-be marketed formulation under maximal use conditions) in patients in parallel with the clinical efficacy studies.

(b) (4)



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/s/

Stanka Kukich
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