

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204708Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 204708

SUPPL #

HFD # 540

Trade Name Mirvaso

Generic Name (brimonidine) topical gel, 0.33%

Applicant Name Galderma Research and Development

Approval Date, If Known 8/23/2013 (PDUFA)

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)(2)

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.

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:

d) Did the applicant request exclusivity?

YES NO

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

3 years

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?

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# 020613

Alphagan (brimonidine tartrate) Ophthalmic Solution, 0.2%

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:

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	18140	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	18141	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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

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	18140	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	18141	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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"):

18140 and 18141

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 18140 !
IND # 074841 YES ! NO
! Explain:

Investigation #2 18141 !
IND # 074841 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 ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! 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: Dawn Williams
Title: RPM
Date: 6/19/2013

Name of Division Director signing form: Susan J. Walker, MD, FAAD
Title: Director, DDDP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

DAWN WILLIAMS
08/22/2013

SUSAN J WALKER
08/22/2013

1.3.3 Debarment certification
Page 1 of 1

1.3.3 DEBARMENT CERTIFICATION

In accordance with the requirements of the Federal Food, Drug and Cosmetic Act section 306(k)(1), the Applicant, Galderma Research and Development Inc., 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 New Drug Application 204708 for Brimonidine Tartrate 0.5% Gel.

Sep 27, 2012
Date


Signature

Elaine Clark
Senior Director, US Regulatory Submissions

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

NDA/BLA#: 204708 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____
Division Name: DDDP PDUFA Goal Date: _____ Stamp Date: 10/25/2013
8/25/2013

Proprietary Name: Mirvaso

Established/Generic Name: (brimonidine tartrate)

Dosage Form: Gel, 0.5%

Applicant/Sponsor: Galderma Research and Development Inc.

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

- (1) N/A
(2) _____
(3) _____
(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: Treatment of facial erythema of rosacea in adult patients 18 years of age and older

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 †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<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 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 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)

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.

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 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.

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 204708 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Mirvaso Established/Proper Name: (brimonidine) Dosage Form: topical gel, 0.33%		Applicant: Galderma Resarach and Development Agent for Applicant (if applicable):
RPM: Dawn Williams		Division: DDDP
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" 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 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>NDA 020613 Alphagan (brimonidine tartrate) Ophthalmic Solution, 0.2%</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>The indications, dosage forms, and dosing regimens are different</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input checked="" type="checkbox"/> This application relies on (explain) the Agency's finding of safety and effectiveness of NDA 020613 to support some nonclinical portions of this application.</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></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>	
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>August 25, 2013</u> 	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR	
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 	<input type="checkbox"/> None	

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.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><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</p> <p>NDA: 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</p> <p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<p><input checked="" 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</p>

³ Answer all questions in all sections in relation 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 BLAs: 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 checked="" 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 checked="" 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 checked="" 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 checked="" 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 checked="" 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 checked="" 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 checked="" 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 checked="" 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>	<input type="checkbox"/> Yes <input type="checkbox"/> No
---	--

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	Yes
Officer/Employee List	
❖ 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>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Approval August 23, 2013
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	FPI- 8-20-2013 (Agreed Upon)
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	10/25/2013
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert (submitted June 19, 2013) <input checked="" type="checkbox"/> Instructions for Use (submitted June 19, 2013) <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	Agreed upon FPI, PPI and IFU August 20, 2013
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	FPI October 25, 2012; PPI and IFU June 19, 2013
<ul style="list-style-type: none"> • Example of 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 draft labeling 	Agreed upon August 21, 2013
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • <i>Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</i> 	July 25, 2013 Proprietary Name Review March 7, 2013 Proprietary Name Granted; March 5, 2013 Proprietary Name Review
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM August 21, 2013 <input checked="" type="checkbox"/> DMEPA March 27, 2013 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) July 9, 2013 <input checked="" type="checkbox"/> ODPD (DDMAC) May 9, 2013 <input checked="" type="checkbox"/> SEALD August 19, 2013 <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 Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	January 15, 2013 RPM Filing Review
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2) June 24, 2013 <input type="checkbox"/> Not a (b)(2) July 1, 2013
<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 is 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 type="checkbox"/> No <input type="checkbox"/> Not an AP action

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>June 5, 2013</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
❖ 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
❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	May 28, 2013 Information Request; May 13, 2013 Information Request; December 13, 2012 No Filing Issues Identified; November 29, 2013 Information Request; November 20, 2012 Acknowledgement; November 15, 2012 Information Request
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg May 16, 2012
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg March 10, 2008
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	August 9, 2006 Pre-IND
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 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>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None August 21, 2013
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None August 19, 2013
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	
• Clinical review(s) (<i>indicate date for each review</i>)	June 24, 2013 Clinical Review; January 8, 2013 Clinical Filing Review

⁶ Filing reviews should be filed with the discipline reviews.

<ul style="list-style-type: none"> • Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i> 	<input type="checkbox"/> None
<ul style="list-style-type: none"> ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i> 	Pages 15-17 of June 24, 2013 Clinical Review
<ul style="list-style-type: none"> ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i> 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> ❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i> 	<input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> ❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and Supporting Statement <i>(indicate date(s) of submission(s))</i> • REMS Memo(s) and letter(s) <i>(indicate date(s))</i> • Risk management 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
<ul style="list-style-type: none"> ❖ OSI Clinical Inspection Review Summary(ies) <i>(include copies of OSI letters to investigators)</i> 	<input type="checkbox"/> None requested June 7, 2013 OSI Summary; June 4, 2013 NAI; May 21, 2013 NAI; May 14, 2013 NAI; May 14, 2013 VAI
Clinical Microbiology <input checked="" type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i> 	<input type="checkbox"/> None
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i> 	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None June 11, 2013 Review; December 11, 2012 Filing Review
Clinical Pharmacology <input type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i> 	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None April 25, 2013 Review; December 4, 2012 Filing Review
<ul style="list-style-type: none"> ❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i> 	<input checked="" type="checkbox"/> None

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None April 25, 2013 Review; November 28, 2012 Filing Review
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input type="checkbox"/> No carc March 27, 2013
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None March 26, 2013 Included in P/T review, page 21-23
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None August 21, 2013 CMC Addendum; June 21, 2013 CMC Review; December 10, 2013 Filing Review
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ 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</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Page 78 of June 21, 2013 CMC Review
<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	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) (date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites ⁷)	Date completed: December 27, 2012 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (check box only, do not include documents)	<input checked="" type="checkbox"/> Completed – Page 40 June 21, 2013 CMC Review <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix 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.

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

/s/

DAWN WILLIAMS
08/23/2013

From: Williams, Dawn
Sent: Wednesday, August 21, 2013 6:51 AM
To: 'CLARK Elaine'
Cc: Gould, Barbara
Subject: Carton and Container Labels NDA 204708 Mirvaso (brimonidine) topical gel, 0.33%

Good Morning Elaine-

We noted that the carton and container labels (all presentations) listed the URL www.mirvaso.com. Since we removed this from the FPI, we'd like it removed from the carton and container labels. Could you please re-submit the carton and container labels once this revision has been made?

It appears that we have agreement on the FPI, PPI, and IFU that were submitted yesterday.
Thank you!

CDR Dawn Williams, BSN, USPHS
Division of Dermatology and Dental Products, Room 5164
Office of Drug Evaluation III
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Silver Spring, MD 20993
Tel. (301)796-5376
Fax (301)796-9894

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

/s/

DAWN WILLIAMS
08/21/2013

From: Williams, Dawn
Sent: Monday, August 19, 2013 1:53 PM
To: 'CLARK Elaine'
Cc: Gould, Barbara
Subject: FDA Labeling Proposal 8-19-2013 NDA Mirvaso (brimonidine) topical gel, 0.33%

Good Afternoon Elaine-

As per our conversation, please see the attachments for our most recent labeling proposal. Also, please see below for our most recent carton and container label comments, and provide your response by noon tomorrow. Thank you!

The container carton labels should be modified as follows:

- 1) The established name, administration route and strength of the drug product should be displayed as shown below:

[Redacted] (b) (4)

- 2) The description [Redacted] (b) (4) with the **inactive** ingredients.....' should be modified to display as follows:

[Redacted] (b) (4)



FDA proposal 8-19-2013 FPI NDA 204708.pdf



FDA Proposal 8-19-2013 IFU NDA 204708.pdf



FDA Proposal 8-19-2013 PPI NDA 204708.pdf

CDR Dawn Williams, BSN, USPHS
Division of Dermatology and Dental Products, Room 5164
Office of Drug Evaluation III
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Silver Spring, MD 20993
Tel. (301)796-5376
Fax (301)796-9894

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

/s/

DAWN WILLIAMS
08/19/2013

From: Williams, Dawn
Sent: Friday, August 16, 2013 6:57 AM
To: 'CLARK Elaine'
Cc: Gould, Barbara
Subject: FDA Labeling Proposal 8-16-2013 NDA 204708 Mirvaso (brimonidine) Gel, 0.33%

Good Morning Elaine-

Attached are the most recent FDA FPI, PPI and IFU proposals for NDA 204708 Mirvaso (brimonidine) Gel, 0.33%. Please provide your response by noon on Monday, August 19, 2013. Thank you!

CDR Dawn Williams, BSN, USPHS
Division of Dermatology and Dental Products, Room 5164
Office of Drug Evaluation III
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Silver Spring, MD 20993
Tel. (301)796-5376
Fax (301)796-9894



FDA proposal 8-16-2013 FPI NDA 204708.pdf



FDA proposal 8-16-2013 IFU NDA 204708.pdf



FDA proposal 8-16-2013 PPI NDA 204708.pdf

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

/s/

DAWN WILLIAMS
08/16/2013

From: Williams, Dawn
Sent: Monday, August 12, 2013 10:00 AM
To: 'CLARK Elaine'
Cc: Gould, Barbara
Subject: FDA Labeling Proposal NDA 204708 Mirvaso (brimonidine) Gel, 0.33%

Good Morning Elaine-

Please see the attachments for the FDA's most recent labeling proposal for NDA 204708 Mirvaso (brimonidine) Gel, 0.33%. Please have your response to this proposal by Wednesday, August 14, 2013. It appears that we have agreed upon the carton and container labels (version submitted 8/2/2013). If you have any questions regarding this email, please do not hesitate to contact me. Thank you!

CDR Dawn Williams, BSN, USPHS
Division of Dermatology and Dental Products, Room 5164
Office of Drug Evaluation III
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Silver Spring, MD 20993
Tel. (301)796-5376
Fax (301)796-9894

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

DAWN WILLIAMS
08/12/2013

From: Phillips, J. Paul
Sent: Friday, August 02, 2013 12:53 PM
To: 'CLARK Elaine'
Cc: 'ALMOND Richard'; Gould, Barbara; Williams, Dawn
Subject: NDA 204708 (Mirvaso)

Ms. Clark,

Below are some corrections to the FDA edits sent for the PI for NDA 204708 (Mirvaso).

5.3 Serious Adverse Reactions following Ingestion of MIRVASO Gel

Two young children experienced serious adverse reactions during clinical trials following accidental ingestion of MIRVASO Gel. Adverse reactions experienced by one or both children included lethargy, respiratory distress with apneic episodes (requiring intubation), sinus bradycardia, confusion, psychomotor hyperactivity, and diaphoresis. Both children were hospitalized overnight and discharged the following day without sequelae.

6 ADVERSE REACTIONS

Open-label, Long-term Study

An open-label study (b) (4) -of MIRVASO Gel when applied once daily for up to one year was conducted in subjects with persistent (nontransient) facial erythema of rosacea. Subjects were allowed to use other rosacea therapies. A total of 276 subjects applied MIRVASO Gel for at least one year. The most common adverse events ($\geq 4\%$ of subjects) for the entire study were flushing (10%), erythema (8%), rosacea (5%), nasopharyngitis (5%), skin burning sensation (4%), increased intraocular pressure (4%), and headache (4%).

Allergic contact dermatitis

Allergic contact dermatitis to MIRVASO Gel was reported in approximately 1% of subjects across the clinical development program. Two subjects underwent patch testing with individual product ingredients. One subject was found to be sensitive to brominidine tartrate, and one subject was sensitive to phenoxyethanol (a preservative).

(b) (4)

Thank you.

J. Paul Phillips, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5189
10903 New Hampshire Ave.
Silver Spring, MD 20993

Telephone: (301) 796-3935
Fax: (301) 796-9895
e-mail: Paul.Phillips@fda.hhs.gov

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

/s/

J P PHILLIPS
08/02/2013

From: Phillips, J. Paul
Sent: Wednesday, July 31, 2013 5:09 PM
To: 'CLARK Elaine'
Cc: 'ALMOND Richard'; Gould, Barbara; Williams, Dawn
Subject: NDA 204708 (Mirvaso)

Ms. Clark,

Please see the attached draft labeling for NDA 204708 (Mirvaso) with FDA edits in track changes. We ask that you respond **by 8/7/2013**.



NDA 204708 FDA
FPI Proposal- 1...



NDA 204708 FDA
IFU Proposal- 1...



NDA 204708 FDA
PPI Proposal- 1...

Regards,

J. Paul Phillips, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5189
10903 New Hampshire Ave.
Silver Spring, MD 20993

Telephone: (301) 796-3935
Fax: (301) 796-9895
e-mail: Paul.Phillips@fda.hhs.gov

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

/s/

J P PHILLIPS
07/31/2013

From: Williams, Dawn
Sent: Wednesday, July 24, 2013 9:20 AM
To: 'CLARK Elaine'
Cc: Gould, Barbara; Phillips, J. Paul
Subject: FDA Carton and Container Label Proposal NDA 204708 Mirvaso (brimonidine) Gel, 0.33%

Good Morning Elaine-

Please see our proposal for the carton and container labels for NDA 204708 Mirvaso (brimonidine) Topical Gel, 0.33%, and provide your response by July 31, 2013. Please reply to all that I've "cc'd" on this email with your response. Thank you!

The carton and container label comments are below.



(b) (4)

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

DAWN WILLIAMS
07/24/2013



NDA 204708

INFORMATION REQUEST

Galderma Research and Development
Attention: Elaine Clark
Senior Director, US Regulatory Submissions
5 Cedar Brook Drive; Suite 1
Cranbury, NJ 08512

Dear Ms. Clark:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mirvaso (brimonidine tartrate) Gel, 0.5%.

We are reviewing the labeling of your submission and have the following comment and request for information. We request your response by June 20, 2013, in order to continue our evaluation of your NDA.

With consideration of our previous requests (March 2, 2012 teleconference and April 3, 2012 advice letter under IND 074841) for additional safeguards (labeling and container/closure changes) to lessen the risk from accidental exposure to your product, submit a Patient Package insert.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.
Sincerely,

{See appended electronic signature page}

Brenda Carr, MD
Acting Clinical Team Leader
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/

BRENDA CARR
05/28/2013



NDA 204708

INFORMATION REQUEST

Galderma Research and Development
Attention: Elaine Clark
Senior Director, US Regulatory Submissions
5 Cedar Brook Drive; Suite 1
Cranbury, NJ 08512

Dear Ms. Clark:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mirvaso (brimonidine tartrate) Gel, 0.5%.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by May 15, 2013 in order to continue our evaluation of your NDA.

Drug Product:

1. You have submitted up to 3-month stability study results in the Feb 5, 2013 amendment. Provide, in tabular format, up to 6-months long-term and accelerated stability study results (including weight data) for the three drug product batches (30 g and 45 g tubes) packaged in child-resistant container closure system.
2. Provide weight loss data for each registration stability batch and each packaging configuration.
3. Add the following statement to the post approval stability commitment in Section 3.2.P.8.2., and submit an updated Section 3.2.P.8.2.
 - Galderma agrees to withdraw from the market any lots that fall outside the approved drug product specifications. If existing evidence indicates that the deviation is a single occurrence that does not affect the safety and efficacy of the drug product, Galderma agrees to immediately discuss it with the reviewing division and provide justification for the continued distribution of that batch. Galderma agrees to comply with the reporting requirements delineated under 21 CFR 314.81(b)(1)(ii).

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, MD, FAAD
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 J WALKER
05/13/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204708

(E) CAC – FINAL REPORT

Galderma Research and Development
Attention: Elaine Clark
Senior Director, US Regulatory Submissions
5 Cedar Brook Drive; Suite 1
Cranbury, NJ 08512

Dear Ms. Clark:

Please refer to your new drug application (NDA pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Mirvaso (brimonidine tartrate) Gel, 0.5%.

Our Executive Carcinogenicity Assessment Committee (ECAC) reviewed your study report on March 26, 2013. As requested in your October 25, 2012 submission, a copy of the final report of the ECAC regarding Mirvaso (brimonidine tartrate) Gel, 0.5% is enclosed.

The recommendations made by the ECAC are advisory in nature and should not be interpreted as a measure of the approvability of any application for this product.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Barbara Hill, PhD
Pharmacology Supervisor
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: ECAC Meeting Minutes

Executive CAC

Date of Meeting: March 26, 2013

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Paul Brown, Ph.D., OND, IO, Member
Albert Defelice, Ph.D., DCRP, Alternate Member
Barbara Hill, Ph.D., DDDP, Supervisor
Jianyong Wang, Ph.D., DDDP, Presenting Reviewer

Author of Draft: Jianyong Wang, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 204708
Drug Name: MIRVASO (brimonidine tartrate) Gel, 0.5%
Sponsor: Galderma Research and Development, Inc., Cranbury, NJ

Background:

MIRVASO Gel, 0.5% is an alpha adrenergic receptor agonist being developed for the treatment of facial erythema of rosacea. The sponsor originally submitted a 2-year dermal rat carcinogenicity protocol for review on 12/20/2007. This protocol did not receive Exec CAC concurrence because there was no adequate dose-ranging data to support dose selection. The sponsor initiated a 2-year dermal rat carcinogenicity study without receiving Exec CAC concurrence. Part of that study generated data for a 13-week dermal rat dose range-finding study and the dose range-finding study was submitted with a new 2-year dermal carcinogenicity study protocol on 01/21/2009. The Exec CAC meeting recommendations and conclusions were relayed to the sponsor on 03/05/2009. The sponsor initiated the 2-year dermal rat carcinogenicity study following the Committee's recommendations.

On 09/15/2010, the sponsor submitted a request for study protocol modification, based on an increase in mortality in mid dose and high dose females at Week 41 of the study. The sponsor was advised to reduce the concentrations of brimonidine tartrate gel for the mid and high dose females on 09/24/2010. On 09/08/2011, the sponsor submitted another request for study protocol modification based on a low survival rate noted in the high dose female group at Week 92. The sponsor was provided with guidance on appropriate dose group termination criteria on 10/05/2011. The 2-year dermal rat carcinogenicity study was completed on 09/27/2012. The final study report was submitted to NDA 204708 on 10/25/2012.

Rat Carcinogenicity Study:

In a 2-year dermal rat carcinogenicity study, topical doses of 0 (water control), 0 (vehicle control), 0.9, 1.8, and 5.4 mg/kg/day brimonidine tartrate (0.03%, 0.06%, and 0.18% gel applied to 20% BSA once daily at 3 ml/kg) were administered to males. Initially topical doses of 0 (water control), 0 (vehicle control), 5.4, 30, and 60 mg/kg/day brimonidine tartrate (0.18%, 1%, and 2% gel applied to 20% BSA once daily at 3 ml/kg) were administered to females. Due to higher mortality rate noted in mid dose and high dose female groups, topical doses for mid dose

and high dose females were reduced to 10.8 and 21.6 mg/kg/day (0.36%, and 0.72% gel applied to 20% BSA once daily at 3 ml/kg), respectively, on Day 343 and thereafter. The vehicle gel contained (b) (4) methylparaben (b) (4), phenoxyethanol (b) (4), glycerin (b) (4), titanium dioxide (b) (4), propylene glycol (b) (4), sodium hydroxide (b) (4) and purified water (b) (4).

After dose reduction for mid dose and high dose females, mortality occurred at comparable rates among all groups. At the end of study survival rate was higher than 50% in all groups except the high dose female group (survival rate 40%). Survival rate at the end of the study was considered acceptable for study interpretation. Body weight in high dose males was lower over the duration of treatment, compared to both the water and vehicle controls (15-18%). In females, body weight was lower in all treated groups over the duration of treatment (16-25%), compared to both the water and vehicle controls. There was no significant test article-related skin irritation. There were no significant test article-related effects on hematology parameters.

For histopathological examination, a complete list of tissues was examined for all main study animals. There were no significant test article-related non-neoplastic findings in either sex. There were no significant findings in the pair-wise comparison between the water and vehicle control groups in either sex. No statistical significance was achieved in any tumor types in treated males, either in the trend analysis or in pair-wise comparisons to vehicle control. The only statistically significant finding was the incidence of schwannoma in abdominal cavity in high dose females (incidence 2/60). The incidence of schwannoma in high dose females was statistically significant in the trend analysis (p value = 0.04), but not in the pair-wise comparison to vehicle control (p = 0.185). Schwannoma was also noted in abdominal cavity in the male vehicle control group, with an incidence of 1/60. Dietary carcinogenicity studies have been conducted for brimonidine tartrate. No compound-related carcinogenic effects were observed in either a 21-month dietary mouse carcinogenicity study (doses up to 2.5 mg/kg/day) or a 24-month dietary rat carcinogenicity study (doses up to 1.0 mg/kg/day). The finding of schwannoma in abdominal cavity in high dose females in this study is considered biologically insignificant. Overall there were no significant test article-related neoplastic findings, under the study conditions.

Executive CAC Recommendations and Conclusions:

- The Committee concluded that the study was acceptable.
- The Committee concurred that there were no drug-related neoplasms in the dermal rat carcinogenicity study.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\

/Division File, DDDP

/B. Hill, Supervisor, DDDP

/J. Wang, P/T reviewer, DDDP

/D. Williams, Project Manager, DDDP

/A. Seifried, 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/

BARBARA A HILL
04/17/2013

Executive CAC

Date of Meeting: March 26, 2013

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Paul Brown, Ph.D., OND, IO, Member
Albert Defelice, Ph.D., DCRP, Alternate Member
Barbara Hill, Ph.D., DDDP, Supervisor
Jianyong Wang, Ph.D., DDDP, Presenting Reviewer

Author of Draft: Jianyong Wang, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 204708
Drug Name: MIRVASO (brimonidine tartrate) Gel, 0.5%
Sponsor: Galderma Research and Development, Inc., Cranbury, NJ

Background:

MIRVASO Gel, 0.5% is an alpha adrenergic receptor agonist being developed for the treatment of facial erythema of rosacea. The sponsor originally submitted a 2-year dermal rat carcinogenicity protocol for review on 12/20/2007. This protocol did not receive Exec CAC concurrence because there was no adequate dose-ranging data to support dose selection. The sponsor initiated a 2-year dermal rat carcinogenicity study without receiving Exec CAC concurrence. Part of that study generated data for a 13-week dermal rat dose range-finding study and the dose range-finding study was submitted with a new 2-year dermal carcinogenicity study protocol on 01/21/2009. The Exec CAC meeting recommendations and conclusions were relayed to the sponsor on 03/05/2009. The sponsor initiated the 2-year dermal rat carcinogenicity study following the Committee's recommendations.

On 09/15/2010, the sponsor submitted a request for study protocol modification, based on an increase in mortality in mid dose and high dose females at Week 41 of the study. The sponsor was advised to reduce the concentrations of brimonidine tartrate gel for the mid and high dose females on 09/24/2010. On 09/08/2011, the sponsor submitted another request for study protocol modification based on a low survival rate noted in the high dose female group at Week 92. The sponsor was provided with guidance on appropriate dose group termination criteria on 10/05/2011. The 2-year dermal rat carcinogenicity study was completed on 09/27/2012. The final study report was submitted to NDA 204708 on 10/25/2012.

Rat Carcinogenicity Study:

In a 2-year dermal rat carcinogenicity study, topical doses of 0 (water control), 0 (vehicle control), 0.9, 1.8, and 5.4 mg/kg/day brimonidine tartrate (0.03%, 0.06%, and 0.18% gel applied to 20% BSA once daily at 3 ml/kg) were administered to males. Initially topical doses of 0 (water control), 0 (vehicle control), 5.4, 30, and 60 mg/kg/day brimonidine tartrate (0.18%, 1%,

and 2% gel applied to 20% BSA once daily at 3 ml/kg) were administered to females. Due to higher mortality rate noted in mid dose and high dose female groups, topical doses for mid dose and high dose females were reduced to 10.8 and 21.6 mg/kg/day (0.36%, and 0.72% gel applied to 20% BSA once daily at 3 ml/kg), respectively, on Day 343 and thereafter. The vehicle gel contained (b) (4) methylparaben (b) (4), phenoxyethanol (b) (4), glycerin (b) (4), titanium dioxide (b) (4), propylene glycol (b) (4), sodium hydroxide (b) (4) and purified water (b) (4).

After dose reduction for mid dose and high dose females, mortality occurred at comparable rates among all groups. At the end of study survival rate was higher than 50% in all groups except the high dose female group (survival rate 40%). Survival rate at the end of the study was considered acceptable for study interpretation. Body weight in high dose males was lower over the duration of treatment, compared to both the water and vehicle controls (15-18%). In females, body weight was lower in all treated groups over the duration of treatment (16-25%), compared to both the water and vehicle controls. There was no significant test article-related skin irritation. There were no significant test article-related effects on hematology parameters.

For histopathological examination, a complete list of tissues was examined for all main study animals. There were no significant test article-related non-neoplastic findings in either sex. There were no significant findings in the pair-wise comparison between the water and vehicle control groups in either sex. No statistical significance was achieved in any tumor types in treated males, either in the trend analysis or in pair-wise comparisons to vehicle control. The only statistically significant finding was the incidence of schwannoma in abdominal cavity in high dose females (incidence 2/60). The incidence of schwannoma in high dose females was statistically significant in the trend analysis (p value = 0.04), but not in the pair-wise comparison to vehicle control (p = 0.185). Schwannoma was also noted in abdominal cavity in the male vehicle control group, with an incidence of 1/60. Dietary carcinogenicity studies have been conducted for brimonidine tartrate. No compound-related carcinogenic effects were observed in either a 21-month dietary mouse carcinogenicity study (doses up to 2.5 mg/kg/day) or a 24-month dietary rat carcinogenicity study (doses up to 1.0 mg/kg/day). The finding of schwannoma in abdominal cavity in high dose females in this study is considered biologically insignificant. Overall there were no significant test article-related neoplastic findings, under the study conditions.

Executive CAC Recommendations and Conclusions:

- The Committee concluded that the study was acceptable.
- The Committee concurred that there were no drug-related neoplasms in the dermal rat carcinogenicity study.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\n
/Division File, DDDP
/B. Hill, Supervisor, DDDP
/J. Wang, P/T reviewer, DDDP
/D. Williams, Project Manager, DDDP
/A. Seifried, 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/

ADELE S SEIFRIED
03/27/2013

DAVID JACOBSON KRAM
03/27/2013



NDA 204708

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Galderma Laboratories, L.P.
14501 North Freeway
Forth Worth, TX 76177

ATTENTION: Elaine Clark
Senior Director, US Regulatory Submissions

Dear Ms. Clark:

Please refer to your New Drug Application (NDA) dated October 25, 2012, received October 25, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brimonidine Tartrate Topical Gel, 0.5%.

We also refer to your December 7, 2012, correspondence, received December 7, 2012, requesting review of your proposed proprietary name, Mirvaso. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Mirvaso, will be re-reviewed 90 days prior to the approval of the NDA. 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 December 7, 2012 submission are altered prior to approval of the marketing application, the 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 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 Office of New Drugs (OND) Regulatory Project Manager, Dawn Williams at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
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/

CAROL A HOLQUIST
03/07/2013



NDA 204708

FILING COMMUNICATION

Galderma Research and Development
Attention: Elaine Clark
Senior Director, US Regulatory Submissions
5 Cedar Brook Drive; Suite 1
Cranbury, NJ 08512

Dear Ms. Clark:

Please refer to your New Drug Application (NDA) dated and received October 25, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Mirvaso (brimonidine tartrate) Gel, 0.5%.

We also refer to your amendments dated November 21, and December 3, 2012.

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 August 25, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by August 1, 2013.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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

We 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 Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, MD, FAAD
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 J WALKER
12/13/2012



NDA 204708

INFORMATION REQUEST

Galderma Research and Development, Inc.
Attention: Elaine Clark
Senior Director, US Regulatory Submissions
14501 North Freeway
Fort Worth, TX 76177

Dear Ms. Clark:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brimonidine Tartrate, 0.5% Gel.

We also refer to your October 26, 2012 submission, containing information for an original new drug application.

We are reviewing the Chemistry, Manufacturing and Control section 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.

1. Submit the proposed drug product regulatory specification to Section 3.2.P.5.1. Currently, only the release specification is in Section .2.P.5.1. The Agency does not consider the release specification as the regulatory specification unless you clearly state so and state that the proposed stability specification is the same as the proposed release specification.
2. Submit stand alone method validation package to Section 3.2.R.3 per 21 CFR 314.50 (e)(2)(i).
3. Submit Master Batch Records that are to be used for the manufacture of drug product commercial batches.

If you have any questions, call Cathy Tran-Zwanetz, Regulatory Project Manager, at (301) 796-3877.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Branch Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
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/

MOO JHONG RHEE
11/29/2012
Chief, Branch IV



NDA 204708

NDA ACKNOWLEDGMENT

Galderma Research and Development Inc.
Attention: Elaine Clark
Sr. Director, US Regulatory Submissions
14501 North Freeway
Fort Worth, TX 76177

Dear Ms. Clark:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Mirvaso (brimonidine tartrate) Topical Gel, 0.5%

Date of Application: October 25, 2012

Date of Receipt: October 25, 2012

Our Reference Number: NDA 204708

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 December 24, 2012, 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/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. 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.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

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/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Dawn Williams, BSN
Regulatory Health Project Manager
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/

DAWN WILLIAMS
11/20/2012



NDA 204708

INFORMATION REQUEST

Galderma Research and Development
Attention: Elaine Clark
Senior Director, US Regulatory Submissions
5 Cedar Brook Drive, Suite 1
Cranbury, NJ 08512

Dear Ms. Clark:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (brimonidine tartrate) Gel, 0.5%.

We are reviewing the nonclinical section of your submission and have the following comments and information requests. We request a prompt written response by November 22, 2012, in order to continue our evaluation of your NDA.

As relayed to you during the Pre-NDA meeting on 05/16/2012 (contained in the response to Question 10), the tumor dataset for the 2-year dermal rat carcinogenicity study should be submitted in conformance to the electronic format specified in the provided guidance documents. You have not provided an acceptable SAS tumor dataset for the 2-year dermal rat carcinogenicity study in your NDA submission. Therefore, your NDA submission is considered incomplete at this time. Provide the requested tumor dataset by COB 11/22/2012. A document is provided to reiterate the requested dataset formats.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376

Sincerely,

{See appended electronic signature page}

Barbara Hill, PhD
Pharmacology Supervisor
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:

Carci Data Format and Stat Guidance Info Sheets

Office of Biostatistics Information Sheet for Submission of Data and for Methods of Data Analysis of Carcinogenicity Studies

(The electronic data format is for two-year studies as well as transgenic mouse studies using all except the TgAC mouse models)

Revised 07/16/2009

The statistical reviewer responsible for the review of the carcinogenicity studies of this NDA/IND submission requests that the sponsor recreate the tumor data in conformance to the electronic format specified in the Agency's April 2008 guidance document entitled "*Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications*". The guidance document can be found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>. The cover page of the document is attached to this information sheet (Attachment A).

In Section III.D.3 of the above document the Agency gives a general description of the data formats for the pharmacology and toxicology datasets and refers readers to the associated document "*Study Data Specifications*" for more information about the format specifications of the data submission. This associated document can be found at the FDA website <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163561.pdf>. At this time, we are only requesting the tumor dataset in the format described on page 7 (APPENDIX 1) of the associated document. The table containing the format for tumor data in the document is attached to this information sheet (Attachment B).

Please contact the Agency to provide a time line regarding providing the tumor data. The sponsor needs to carefully meet the data format specifications in order to comply with the above guidance. Any data without 100% conformity will have to be returned for resubmission.

Note that the draft guidance for the statistical analysis of chronic rodent carcinogenicity studies is available on the FDA web site at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079272.pdf>. Sponsors are urged to use the statistical methods recommended in the guidance to analyze the carcinogenicity study data in their IND or NDA submissions. The cover page of the document is also attached to this information sheet (Attachment C).

For questions related to the data format and the methods of statistical analysis, please contact Karl K. Lin, Ph.D., Room 4670, Building 21, Office of Biostatistics, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, 301-796-0943, karl.lin@fda.hhs.gov.

(Attachment A)

Cover page of "Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications"

Guidance for Industry

Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**June 2008
Electronic Submissions**

Revision 2

(Attachment B)

Data format table on page 7 (APPENDIX 1) of the associated document "Study Data Specifications"

Tumor Dataset For Statistical Analysis^{1,2} (tumor.xpt)				
Variable	Label	Type	Codes	Comments
STUDYNUM	Study number	char		³
ANIMLNUM	Animal number	char		1,3
SPECIES	Animal species	char	M=mouse R=rat	
SEX	Sex	char	M=male F=female	
DOSEGP	Dose group	num	Use 0, 1, 2, 3,4,... in ascending order from control. Provide the dosing for each group.	
DTHSACTM	Time in days to death or sacrifice	num		
DTHSACST	Death or sacrifice status	num	1 = Natural death or moribund sacrifice 2 = Terminal sacrifice 3 = Planned intermittent sacrifice 4= Accidental death	
ANIMLEXM	Animal microscopic examination code	num	0= No tissues were examined 1 = At least one tissue was examined	
TUMORCOD	Tumor type code	char		3,4
TUMORNAM	Tumor name	char		3,4
ORGANCOD	Organ/tissue code	char		3,5
ORGANNAM	Organ/tissue name	char		3,5
DETECTTM	Time in days of detection of tumor	num		
MALIGNST	Malignancy status	num	1 = Malignant 2= Benign 3 = Undetermined	⁴
DEATHCAU	Cause of death	num	1 = Tumor caused death 2= Tumor did not cause death 3 = Undetermined	⁴
ORGANEXM	Organ/Tissue microscopic examination code	num	1 = Organ/Tissue was examined and was usable 2= Organ/Tissue was examined but was not usable (e.g., autolyzed tissue) 3 = Organ/Tissue was not examined	

¹ Each animal in the study should have at least one record even if it does not have a tumor.

² Additional variables, as appropriate, can be added to the bottom of this dataset.

³ ANIMLNUM is limited to no more than 12 characters; ORGANCOD and TUMORCOD are limited to no more than 8 characters; ORGANNAM and TUMORNAM should be as concise as possible.

⁴ A missing value should be given for the variable MALIGNST, DEATHCAU, TUMORNAM and TUMORCOD when the organ is unusable or not examined.

⁵ Do not include a record for an organ that was useable and no tumor was found on examination. A record should be included for organs with a tumor, organs found unusable, and organs not examined.

(Attachment C)

Cover page of "Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals"

Guidance for Industry

Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. All comments should be identified with the docket number listed in the notice of availability.

For questions regarding this draft document contact (CDER) Karl K. Lin, Ph.D., 301-796-0943, e-mail link.lin@fda.hhs.gov or link@cder.fda.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2001

Pharm/Tox

C:\Data\My Documents #1 A-M\Guidance\04232001\NneyDerr.DOC
11/22/05

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

/s/

BARBARA A HILL
11/15/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 074841

MEETING MINUTES

Galderma Research & Development Inc.
Attention: Elaine Clark
Senior Director, US Regulatory Submissions
5 Cedar Brook Drive, Suite 1
Cranbury, NJ 08512

Dear Ms. Clark:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for COL-118 (brimonidine tartrate) Topical Gel.

We also refer to the meeting between representatives of your firm and the FDA on May 16, 2012. The purpose of the meeting was to discuss the content and format of your planned NDA submission.

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

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Jill Lindstrom, MD
Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA Meeting

Meeting Date and Time: May 16, 2012; 9:00 am
Meeting Location: FDA White Oak Campus, Building 22, Room 1311

Application Number: IND 074841
Product Name: COL-118 (brimonidine tartrate) Topical Gel
Indication: Topical treatment of erythematous rosacea
Sponsor Name: Galderma Research and Development Inc.

Meeting Chair: Jill Lindstrom, MD
Meeting Recorder: Dawn Williams, BSN

FDA ATTENDEES

Jill Lindstrom, MD, Clinical Team Leader, DDDP
Jane Liedtka, MD, Clinical Reviewer, DDDP
Stanka Kukich, MD, Deputy Director, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Jianyong Wang, PhD, Pharmacology Reviewer, DDDP
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP
Dawn Williams, BSN, Regulatory Health Project Manager, DDDP
Strother Dixon, Regulatory Health Project Manager, DDDP
Mohamed Alesh, PhD, Biostatistics Team Leader, DB III
Matthew Guerra, PhD, Biostatistics Reviewer, DB III
Shulin Ding, PhD, Pharmaceutical Assessment Lead, DNDQA II
Gene Holbert, PhD, Product Quality Reviewer, DNDQA II, Branch IV
Victoria Kusiak, MD, Deputy Director, ODE III
Doanh Tran, PhD, Clinical Pharmacology Team Leader, DCP III
Roy Blay, PhD, Regulatory Reviewer, OC

SPONSOR ATTENDEES

Will Boshnell, Consulting Statistician
Maryse Corroller, Regulatory Project Manager
Jesse Kooker, Head Data Management
Nathalie Wagner, Clinical PK Developer
Michael Graeber, Developmental Site Director

Matt Leoni, Medical Advisor
Elaine Clark, Senior Director US Regulatory Submissions
Thierry Bilbault, Industrial Development Director
Guy Bouvier, Preclinical Coordination Manager
Martine Ortega, Regulatory Affairs Project Group Manager

Regulatory Correspondence History

We have had the following meetings with you:

- April 27, 2010 Guidance Meeting
- December 3, 2008 Guidance Meeting
- March 10, 2008 End of Phase 2 Meeting
- October 31, 2007 Guidance Meeting
- August 9, 2006 Pre-IND Meeting

We have sent the following correspondences:

- April 3, 2012 Advice
- October 5, 2011 Advice/Information Request
- September 15, 2011 Advice/Information Request
- March 30, 2011 Special Protocol Agreement
- March 16, 2011 Advice/Information Request
- December 2, 2010 Advice/Information Request
- November 5, 2010 Advice/Information Request
- September 24, 2010 Advice
- August 13, 2010 Information Request
- December 17, 2009 Advice
- September 25, 2009 Advice/Information Request
- September 20, 2009 Advice
- March 5, 2009 Special Protocol Agreement (CARC)

Question 1:

Does the Agency agree that the proposed NDA may be submitted as a 505(b)(2) application with reference to the proposed listed drugs?

Response:

Standard background information:

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf> . In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://inside.fda.gov:9003/downloads/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027521.pdf>) .

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s).

You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of a listed drug for which FDA has made a finding of safety and effectiveness and therefore, you may only rely upon a listed drug that is the subject of an NDA approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). An application approved under section 505(j) of the FD&C Act may not be cited as a listed drug. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you choose to rely on FDA's finding of safety and/or effectiveness for a discontinued listed drug(s) and intend to support the scientific appropriateness of reliance through a comparative study, it is appropriate to use the ANDA product designated as the RLD in the Orange Book as the comparator in a comparative clinical trial to establish a bridge between your proposed drug product and the specified listed drug(s). Note also that reliance on FDA's finding of safety and/or effectiveness for a discontinued listed drug(s) is contingent on FDA's finding that the drug was not discontinued for reasons of safety or effectiveness.

Be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed

product would be a duplicate of that drug and eligible for approval under section 505(j) of the act, we may refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

Question 2:

Based on the draft Table of Contents provided, does the Agency agree that the proposed NDA is adequate for submission?

Response:

The adequacy of the submission will be a review issue. However, at this time what you have outlined in your draft Table of Contents appears sufficient.

Question 3:

Does the Agency agree with the proposed format and content of the submission?

Response:

See answer to Question #2.

Question 4:

Background

The proposed indication for (brimonidine tartrate) Gel, 0.5% is for the treatment of facial erythema of rosacea in adult patients 18 years of age and above.

Rosacea is most commonly observed in the adult Caucasian population, and is more commonly observed in women than in men, with onset usually occurring between the ages of 30 and 50 years (Powell F 2005).

There is no systematic overview on the prevalence of pediatric rosacea and very few cases of childhood rosacea have been described in the literature. One study (Chamaillard M et al 2008) examined the medical records of children 1 to 15 years of age that were seen at the Pediatric Dermatology Unit of Bordeaux Children's Hospital between 1 January 1996 and 31 December 2005 (5000 external visits per year; total approximately 50,000 visits), and only 20 cases of rosacea were identified. Furthermore, brimonidine tartrate is known to have an unfavorable safety profile in young children.

Based on the scarcity of reported cases of rosacea in the pediatric population, and the safety profile of brimonidine tartrate in children, the Applicant takes the position that development of (brimonidine tartrate) Gel, 0.5% in the treatment of pediatric rosacea is unfeasible.

Consequently, the Applicant proposes to request a waiver from the requirement to perform clinical studies in a pediatric population, pursuant to section 505B(a)(4)(A)(iii)

of the Pediatric Research Equity Act. The pediatric waiver request will be provided to the Agency in Section 1.9 of the proposed NDA.

Does the Agency agree?

Response:

Yes, a waiver seems reasonable. Also include your rationale, with support, in your NDA.

Question 5:

Background

Based on the historical safety information available for active drug substance, brimonidine tartrate, and on the safety profile observed during the clinical development program, the Applicant considers proposing in Section 1.16 of the proposed NDA, routine risk minimization measures consisting of appropriate labeling and routine post-approval pharmacovigilance monitoring to address the known risks for use of (brimonidine tartrate) Gel, 0.5% in the target population.

Does the Agency agree?

Response:

Yes, this seems reasonable assuming no safety signals are detected during review of your NDA submission.

Question 6:

Background

The Applicant proposed to provide the Agency with all references included in Module 2 of the proposed NDA. All other references included in Modules 1,2,4 and 5, as well as references cited in clinical study reports will be provided upon request.

Does the Agency agree?

Response:

Yes, this seems reasonable.

Question 7:

Background

Brimonidine Tartrate Gel, 0.5% is a novel drug product that offers significant therapeutic innovation for the treatment of facial erythema of rosacea in adult patients 18 years of age and above.

Section 10.6.1 provides a rationale for the classification of (brimonidine tartrate) Gel, 0.5% as a significant therapeutic innovation.

Based on these considerations, the Applicant requests that a priority review classification be assigned by the Division of Dermatology and Dental Products.

Does the Agency agree that (brimonidine tartrate) Gel, 0.5% qualified for a priority review classification?

Response:

No, your product does not appear to meet the criteria for a priority review; however, this will be a review issue at the time of submission.

Question 8:

The Applicant has performed a thorough QT/QTc (TQT) study (SRE.18139) and the final study report is proposed to be included in Section 5.3.5.4 Other Study Reports and Related Information of the dossier (see Appendix 1 Overall Table of Contents).

Does the Agency agree with the location of the thorough QT/QTc study report?

Response:

Yes, this seems reasonable.

Chemistry, Manufacturing and Controls (CMC)

Question 9:

Does the Agency agree with the proposed shelf life?

Response:

The shelf-life to be granted is a review issue.

Additional Comments

1. Provide a representative sample of the 0.5% gel for dosage form evaluation.
2. Provide DMF number with a letter of authorization for each drug substance supplier.
3. Two of the proposed excipients (glycerin and propylene glycol) are described in the CMC section to function (b) (4) in the proposed formulation (p. 89 of 474 of the briefing package). (b) (4) is an *in vivo* skin effect. We recommend that you designate the function of each inactive ingredient based on its physicochemical characteristics.

Meeting Discussion:

The sponsor agreed to provide a sample of the 0.5% gel at the time of NDA submission.

The sponsor agreed to provide DMF numbers with a Letter of Authorization for each drug substance supplier.

The sponsor stated that they do not intend to claim (b) (4) properties for the two proposed excipients, and that the function of the excipients will be noted in the submission.

Addendum:

Additionally, submit a sample of the vehicle test article used in the Phase 3 clinical trials at the time of NDA submission.

Pharmacology/Toxicology

Question 10:

Does the Agency agree that the proposed Pharmacology/Toxicology proprietary studies, the proposed historical data/literature sources, and the FDA's finding of safety for the reference listed drugs on which the 505(b)(2) application will rely, support the submission?

Response:

We agree that no additional nonclinical studies are needed to support your 505(b)(2) application, provided that an adequate clinical bridge is established between your drug product and the listed drug(s).

It should be noted that you cannot directly cite data to which you do not have a right to refer, nor can you reference information from the Summary Basis of Approval (SBA) or FDA reviewers' public summaries for support of safety and/or effectiveness. You may rely only upon the Agency's finding of safety and/or effectiveness as is reflected in the approved labeling for the listed drug(s).

Submit the final study report of the 2-year dermal rat carcinogenicity study with your NDA. The 2-year dermal rat carcinogenicity study report should be submitted in conformance to the electronic format specified in the guidance document "Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications", which can be found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>. The tumor dataset should be submitted in the format (table) described in Appendix 1 of an associated document, "Study Data Specifications", which can be found at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163561.pdf>. Any data without 100% conformity will be returned for resubmission. Draft guidance for the statistical analysis of chronic rodent carcinogenicity studies is available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079272.pdf>.

Meeting Discussion:

The sponsor inquired whether the NDA number and label of the listed drug need to be provided in the NDA. The Agency clarified that this information is not necessary. The sponsor can only rely on the Agency's finding of safety for a listed drug to which a clinical bridge has been established.

The sponsor stated that they plan to submit a sample of tumor data from the 2-year dermal rat carcinogenicity study to confirm conformity prior to the NDA submission. This approach is acceptable.

Clinical Pharmacology/Biopharmaceutics

Question 11:

Does the Agency agree that an adequate clinical bridge has been established between (brimonidine tartrate) Gel, 0.5% and the reference listed drugs on which the 505(b)(2) application relies for approval?

Response:

The adequacy of the bridge will be a review issue.

Include in the NDA raw and calculated pharmacokinetic parameter values for trial RD.06.SRE.18143 in SAS transport format (.XPT).

Clinical/Biostatistics

Question 12:

Based on the draft Tables of Contents provided for Sections 2.7.3 and 2.7.4, does the Agency agree that separate ISE and ISS narratives are not required in the proposed NDA?

Response:

You propose to provide the Agency with Sections 2.7.3 Summary of Clinical Efficacy and 2.7.4 Summary of Clinical Safety that are sufficiently detailed to also serve as the full narrative portions of the Integrated Summary of Clinical Efficacy (ISE) and Integrated Summary of Safety (ISS), respectively, while remaining within the suggested size limitations for Module 2 (i.e., maximum 400 pages for Section 2.7 Clinical Summaries). This appears reasonable.

Question 13:

Background

In accordance with 21 CFR 314.50(f), the Applicant proposed to include the following subject Case Report Forms (CRF's) in the proposed NDA:

- Subject who died
- Subjects who had other serious adverse events
- Subject who prematurely discontinued from studies due to an adverse event, whether or not the event was considered related to the study drug.

Does the Agency agree?

Response:

Yes, this seems reasonable. Also include case report forms for all “severe” local adverse events.

Question 14:

Does the Agency agree with the proposed pooling strategies?

Response:

You propose the following populations:

- Primary population: subjects with rosacea from 4-week well-controlled studies who received Brimonidine Tartrate 0.5% Gel – Studies 18140 (pivotal), 18141(pivotal), and 18161(phase 2b)
- Subjects from the long-term safety study – Study 18142
- Subjects from dose finding studies - Study 18144 (dose-response)
- Subjects from the PK studies - Study 18143
- Subjects from dermal safety studies – Studies 18123, 18124, 18125, 18189

Meeting Discussion:

The sponsor clarified that they propose to include 18 studies in the ISS. The Agency agreed that this approach is acceptable.

ISE

No pooling is planned for efficacy.

You propose that data from the following studies will be presented for efficacy analysis:

- Phase 2a: SRE.18144 PD (Dose-Response) - data for the 0.5% Gel only
- Phase 2b: SRE.18161 - data for the 0.5% Gel only
- Phase 3: SRE.18140 and SRE.18141 (pivotal studies)
- Long-Term Safety: SRE.18142 (open-label)

This strategy for the efficacy analysis seems reasonable.

Provide your rationale for including open-label data in the ISE.

In addition to the above provide the following in the ISE or elsewhere in your submission as appropriate:

1. A detailed examination of study to study differences in results. Critical study design differences should be discussed and compared. The extent to which the results of the relevant studies reinforce or do not reinforce each other. Any major inconsistencies in the data regarding efficacy should be addressed, and any areas needing further exploration should be identified.

2. A rationale for why the data presented represents a demonstration of substantial evidence of effectiveness for the proposed indication.

ISS

For the ISS you propose

Safety data from clinical studies SRE.18140 (pivotal), SRE.18141 (pivotal), and SRE.18161 (phase 2b-subjects dosed with 0.5% Gel QD and Vehicle Gel QD only) will be fully integrated and an ISS compliant analysis will be provided to the Agency. Tables for these integrated analyses will present data in following three columns:

- 0.5% q D -18140 (pivotal), 18141 (pivotal), and 18161
- 0.5% q D - first month of 18142 (open-label long term safety study)
- Vehicle q D - from 18140 (pivotal), 18141 (pivotal), and 18161

This appears reasonable.

In addition to the above provide the following in the ISS or elsewhere in your submission as appropriate:

1. Shift tables for all laboratory values for both outside the normal range and outside the range that is considered clinically significant. Provide the normal range of values for all parameters, the threshold for concern for a clinically significant change and your justification for why this threshold is appropriate (i.e., for CBC provide all of the above for WBC, RBC, % neutrophils, % lymph, % mono, %eos, % baso, Hcb, Hct, MCHC, RDW, PLT, MPV, etc.).
2. Group means for irritancy safety study results.
3. Frequency tables for sensitivity safety study results. Define and justify the threshold for calling a score positive (or negative) for sensitization.

Question 15:

Background

The Applicant proposed to provide the Agency with all SAS programs used to generate efficacy and disposition analyses for the pivotal Phase 3 studies included in the proposed NDA. SAS programs will be provided in ASCII text format (.txt).

Does the Agency agree?

Response:

Your proposal to submit all SAS programs used to generate efficacy and disposition analyses for the pivotal Phase 3 studies appears to be acceptable and will be very helpful. Ensure that the SAS programs are adequately commented. You plan to use the Multiple Imputation (MI)

method as the primary imputation method to impute missing data on CEA and PSA, which involves generating multiple datasets. Instead of submitting the multiple datasets, provide the code including seed number used to implement MI.

Question 16:

Background

The Applicant intends to submit study datasets in accordance with the current Study Data Tabulation Model (SDTM) implementation guide, version 3.1.2, with the accompanying Define.xml. Details of the proposed dataset submission plan are provided in Section 10.4.4 of this briefing package.

Does the Agency agree with the proposed dataset submission plan?

Response:

Your proposal to submit analysis datasets for those studies that support efficacy based on ADaM format and Define.pdf appears to be acceptable. In addition, note that:

- The electronic datasets should be submitted in SAS transport form (.xpt).
- Each analysis dataset should include the treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations (excluding multiple imputation method, see Question 15), both observed and imputed variables should be included and clearly identified.
- The analysis dataset documentation (Define.xml) should include sufficient detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variables used), and descriptions for the codes used in factor variables.

Your proposal to submit the original raw as SAS transport (.xpt), as well as in SDTM Version 3.1.2, with accompanying Define.xml files is acceptable. Definition files for raw datasets should be modeled according to CDISC/SDTM IG. Refer to CDISC's Define.XML page (<http://www.cdisc.org/define-xml>) for assistance/guidance related to creating Define.xml files for CDISC/SDTM data.

You are encouraged to submit sample electronic SDTM datasets to the Agency for testing prior to your NDA submission. Refer to the FDA website on submitting a sample eCTD (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>) for guidance on sending a test submission. Note that the scope of test submissions is limited.

Meeting Discussion:

The sponsor plans to submit the SDTM datasets in advance of NDA submission.

Question 17:

Background

The Applicant proposes to submit clinical study reports prepared by CollaGenex in “Legacy” format (i.e., bookmarked, text searchable, hyperlinked .pdf files). These clinical study reports would not conform to eCTD (b) (4) and would not contain study tagging files. In total, five clinical study reports would be provided in “Legacy” format and the corresponding study numbers are as follows:

- COL-118-BAPK-101
- COL-119-Phototoxicity-104
- COL-118-ROSE-101
- COL-118-ROSE-102
- COL-118-ROSE-201

In addition to the clinical study reports, all data from the five studies listed above will be provided to the Agency in the proposed NDA.

Does the Agency agree?

Response:

This approach seems reasonable.

Question 18:

Would the Agency like to see representative photos submitted in the proposed NDA?

Response:

Yes.

Meeting:

The Agency clarified that all photographs should be submitted in the eCTD format, and requested identification of representative photographs. The Agency noted that the sponsor could email any further questions regarding format to the esubmission staff at esub@cder.fda.gov.

Question 19:

Does the Agency have any further recommendations or directives for the Applicant regarding possible measures to insure child safety?

Response:

As detailed in the Advice Letter sent on April 3, 2012:

1. **Revise the Subject Instructions For Use** for any ongoing or subsequent studies so that the warning statements (b) (4) appear under the heading “Subject Instructions” to increase the prominence of these statements.

2. **Alternate Container Closure System** - Redesign your packaging so that it does not appear similar to toothpaste containers and includes a mechanism to control the flow of drug product that is dispensed for each use, such as a pump or unit dose packaging. Because two children of a subject in your clinical trial RD.06.SPR.18140 mistakenly believed this product was toothpaste, it is possible that look alike containers contributed to this confusion. Your redesigned container should include a child resistant feature.
3. **Child Resistant Closure** - Revise your current container closure system to include a child resistant closure to minimize the risk of accidental exposure and potentially serious outcomes. This type of closure has been implemented in other marketed topical products (i.e. lidocaine/prilocaine).
4. **Container Label** - In addition to completely redesigning your container closure system and adding a child resistant feature, add the statements (b) (4) (b) (4) to the container labels. These statements can minimize the risk of wrong route of administration and accidental exposure if patients follow these warning instructions.
5. **Carton Labeling** - If carton labeling will exist for your commercial product we recommend adding the following warning statements to the carton labeling: (b) (4) (b) (4) on the principal display panel of your product as well.

Meeting Discussion:

The Division acknowledged that a Type C meeting request has been received to discuss the child-resistant container closure.

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, refer to 21 CFR 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.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

MANUFACTURING FACILITIES

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Addendum:

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

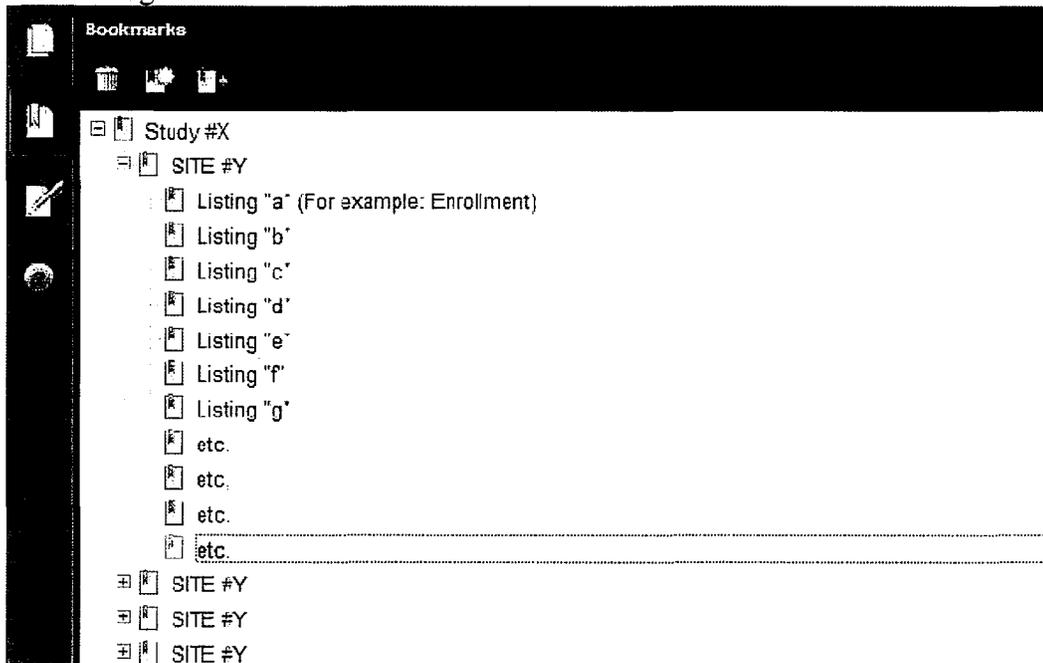
I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
2. Include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:
 - a. Number of subjects screened for each site by site
 - b. Number of subjects randomized for each site by site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
 - a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
 - b. Name, address and contact information of all CROs used in the conduct of the clinical trials
 - c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
 - d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)
4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, describe location or provide a link to requested information).
5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, describe location or provide a link to requested information).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data (“line”) listings. For each site provide line listings for:
 - a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
 - b. Subject listing for treatment assignment (randomization)

- c. Subject listing of drop-outs and subjects that discontinued with date and reason
 - d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of laboratory tests performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Attachment 1, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

Attachment 1

1 Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

1.1 Introduction

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

1.2 Description of the Summary level clinical site dataset

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis

- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)
- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, “TRTEFFR.”

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the “endpoint” plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt).

Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., <u>not limited to only</u> those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount (\$USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount (\$USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parties. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	INITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

IND 074841
Meeting Minutes
Pre-NDA Meeting

ODE III
DDDP

MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

Attachment 2
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD
Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The

¹ Please see the OSI Pre-NDA Request document for a full description of requested data files

leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

IND 074841
Meeting Minutes
Pre-NDA Meeting

ODE III
DDDP

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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
05/23/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 74,841

CollaGenex Pharmaceuticals, Inc.
Attention: Christopher Powala, Vice President
Drug Development & Regulatory Affairs
41 University Drive, Suite 200
Newtown, PA 18940

Dear Mr. Powala:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for COL-118 (brimonidine tartrate) Topical Gel (b) (4) %.

We also refer to the meeting between representatives of your firm and the FDA on March 10, 2008. The purpose of the meeting was to discuss the phase 3 plan and protocols and identify any additional information necessary to support the approval of COL-118 (brimonidine tartrate) Topical Gel (b) (4) % for the treatment of erythema in adult patients with rosacea.

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 Tamika White, Regulatory Project Manager, at (301) 796-0310.

Sincerely,

{See appended electronic signature page}

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

Enclosure

MEMORANDUM OF MEETING MINUTES



Meeting Date: March 10, 2008 **Time:** 9:00 A.M.
Location: WO 22, Room 1313 **Meeting ID:** 23402
Topic: IND 74,841 for COL-118 (brimonidine tartrate)
Topical Gel for the treatment of erythema in adult
patients with rosacea
Subject: End of Phase 2 Meeting
Sponsor: CollaGenex Pharmaceuticals, Inc.
Meeting Chair: Susan J. Walker, M.D./Division Director, DDDP, HFD-540
Meeting Recorder: Tamika White/Regulatory Project Manager, DDDP, HFD-540

FDA Attendees:

Susan J. Walker, M.D./Division Director, DDDP, HFD-540
Jill Lindstrom, M.D./Team Leader, Clinical, Dermatology, DDDP, HFD-540
Gordana Diglisic, M.D./Clinical Reviewer, Dermatology, DDDP, HFD-540
Barbara Hill, Ph.D./Pharmacology Reviewer, DDDP, HFD-540
Shulin Ding, Ph.D./Pharmaceutical Assessment Lead, ONDQA
Gene Holbert, Ph.D./CMC Reviewer, ONDQA
Lydia Velazquez, Pharm.D./Team Leader, Clinical Pharmacology, DPEIII
Tapash Ghosh, Ph.D./Pharmacokinetics Reviewer, DCPIII, HFD-880
Mohamed Al-Osh, Ph.D./Team Leader, Biostatistics, DBIII, HFD-725
Clara Kim, Ph.D./Reviewer, Division of Biometrics III, HFD-725
Margo Owens/Acting Chief, Project Management Staff, DDDP, HFD-540
Tamika White/Regulatory Project Manager, DDDP, HFD-540

Sponsor Attendees:

Christopher Powala/V.P., Drug Development & Regulatory Affairs
Klaus Theobald, M.D., Ph.D./Chief Medical Officer
Shalini Jain/Associate Director, Regulatory Affairs

(b) (4)

Jean Siegel, Ph.D./Regulatory Consultant
Angel Angelov, M.D./Director, Clinical Affairs
Philip Freidenreich, Ph.D./V.P., Quality Assurance & Compliance

Purpose:

To discuss the phase 3 plan and protocols and identify any additional information necessary to support the approval of COL-118 (brimonidine tartrate) Topical Gel (b) (4) % for the treatment of erythema in adult patients with rosacea.

Regulatory

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/cder/guidance/index.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf>)).

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you must establish that reliance on the studies described in the literature is scientifically appropriate. If you intend to rely on the Agency's finding of safety and/or effectiveness for published literature describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

Chemistry, Manufacturing and Controls (CMC)

There are no specific CMC questions and CMC information submitted by the sponsor for this meeting. The CMC reviewer would like to advise the sponsor of the following:

- The Agency's comments conveyed in the 10/31/2007 meeting regarding the testing plan of stability protocol should be implemented before the initiation of registration stability studies.
- Representative samples should be sent to the Agency with justification for dosage form evaluation as soon as possible if not submitted at the meeting.
- The Agency needs more information regarding the role of titanium dioxide in the formulation. The verbal explanation given by the sponsor during the 10/31/07 meeting is not sufficient. Specifically, we need information to support the sponsor's statement that titanium dioxide is an excipient and serves a (b) (4) in the formulation, as titanium dioxide is an active ingredient in other approved products (sunscreens).

Meeting Discussion

The sponsor submitted a sample of the active product and the vehicle during the meeting. The sponsor acknowledged the comments from CMC and will respond in a separate correspondence.

Pharmacology/Toxicology

Question 1:

CollaGenex believes there is ample information to support the deferral of submission of long term dermal carcinogenicity and photocarcinogenicity studies until after COL-118's approval.

With this in mind, the sponsor will initiate the 2-year dermal carcinogenicity in the rat and 52-week photocarcinogenicity study in the hairless mouse. The sponsor plans to file the NDA without the carcinogenicity studies but with a commitment to provide the final reports post-approval.

Does the Division agree with this approach?

Response:

No, we do not agree. Treatment of erythema in adult patients with rosacea is a chronic indication that involves topical treatment to sun exposed skin. Therefore, the evaluation of the dermal carcinogenic potential and photoco-carcinogenic potential of COL-118 gel is needed prior to an NDA submission. The dermal carcinogenic potential or photoco-carcinogenic potential of COL-118 gel have not been evaluated, to date. Therefore, the final study reports for the dermal rodent carcinogenicity study conducted with COL-118 gel and the study to determine the photoco-carcinogenic potential of COL-118 gel conducted in hairless mice should be included with the NDA submission.

Additional comments:

If the sponsor is able to generate an appropriate clinical bridge to the approved Alphagan drug product, then the sponsor would be able to use the Agency's findings of safety for Alphagan to support the safety of their drug product. If the sponsor is not able to generate an appropriate clinical bridge to the approved Alphagan drug product, then the sponsor may be able to obtain right of reference to the approved Alphagan drug product to support the safety of their drug product. In the absence of either a clinical bridge or right of reference letter, the sponsor would need to provide appropriate nonclinical information (i.e., general toxicology, genetic toxicology, reproductive and developmental toxicology and carcinogenicity studies) via conduct of appropriate nonclinical toxicology studies or submission of adequate literature references to support their drug product.

Meeting Discussion

The sponsor stated that they will address this issue in a separate submission. The sponsor disagreed with the Agency's comment that the studies should be completed before the NDA filing.

The Division reemphasized that the photocarcinogenicity and dermal carcinogenicity data should be included with the NDA submission.

Clinical Pharmacology/Biopharmaceutics

Question 5:

The sponsor is willing to obtain additional plasma levels in a subgroup of patients with severe disease in one of the phase 3 studies. The Agency suggested a population PK approach, where each patient would only contribute one blood sample but a variety of post-dosing time points would be captured across patients. The sponsor suggested a blood draw at approximately 1-4 hours post-dose, which is close to the time of peak efficacy observed and suggested that the time between application and the blood draw could be recorded to follow this suggestion. To maintain the blind, samples would be collected for patients with severe disease in both treatment groups and frozen for analysis until after the double-blind portion of the study is clinically complete.

In addition, the treatment regimen has been revised downward for the phase 3 studies to twice daily (BID), rather than 3 times daily (TID). The pharmacokinetic portion of the study can be found in Section 9.7 of Protocol COL-118-ROSE-301.

Does the Division agree with this pharmacokinetic approach?

Response:

Provided the data in the current pharmacokinetic studies confirms what the sponsor claims in this submission, that no detectable plasma levels above 25 pg/ml were observed, and that the phase 2 study used the final to be marketed formulation, the sponsor's blood sampling approach in the planned phase 3 study is acceptable. However, the sponsor should consider that if significant drug exposure is detected in the proposed phase 3 study, another PK trial with multiple PK sampling will be warranted.

Please clarify how many times COL-118 will be applied in the proposed phase 3 study.

We can not accept the submitted phase 2 study as the pivotal PK study since it was not conducted in the targeted patient population and the frequency of dosing was different in the phase 2 trial compared to the proposed phase 3 trial.

The sponsor is advised to conduct an additional phase 2 trial before embarking on any phase 3 trials. The new phase 2 study can incorporate population pharmacokinetics where blood sampling will take place at baseline, then at the one-week and two-week time point.

In order to create a clinical bridge for a 505 (b)(2) application, the sponsor will be required to conduct a cross-over study with the proposed topical gel versus approved 0.2% ocular solution under maximal usage condition in the target patient population. The sponsor is encouraged to share the protocol with the Agency for comments on the design of the protocol.

The label will reflect the amount and the surface area treated. Therefore, the sponsor is required to document amount of gel applied, surface area of application and the frequency of drug application for the proposed study and any other study.

Meeting Discussion

The sponsor will conduct a PK study in rosacea subjects in a cross over design and would monitor IOP and EKGs. They will submit a protocol for review and comment.

The Agency reemphasized that the above study must be conducted under maximal usage conditions. Such a trial would attempt to maximize the potential for drug absorption to occur by incorporation of the following design elements:

- a) Frequency of dosing*
- b) Duration of dosing*
- c) Use of highest proposed strength*
- d) Total involved surface area to be treated at one time*
- e) Amount applied per square centimeter*
- f) Method of application/site preparation*
- g) Sensitive and validated analytical method to measure active and potential metabolite(s).*

The Agency clarified that it is the sponsor's choice on whether to construct the bridge. If the sponsor decides to do so, then they should conduct the additional PK study.

The Agency indicated that the phase 3 protocol was unclear with regards to the number of times applied and the sponsor should clarify how the product should be used.

Clinical/Biostatistics

We note that the following elements have not been resolved since our previous meeting with you (Guidance Meeting, October 31, 2007):

- primary efficacy assessment scales
- primary efficacy endpoints
- global disease assessment scale
- safety assessment:
 - safety monitoring and long term safety assessment

Question 2:

The co-primary endpoints for both clinical trials are as follows:

- Mean change from pre-dose Baseline Clinical Erythema Assessment score (CEA) at Week 4 and mean Patient's Self Assessment Scores (PSA) at Week 4 will be the co-primary efficacy parameters.
- Patient CEA scores from the pre-dose Baseline visit will be subtracted from the Week 4 post-dose CEA scores. The mean of the per-patient changes from Baseline CEA score will be the basis for treatment group comparisons using an analysis of covariance model (ANCOVA) with factors for treatment group and investigator and including pre-dose baseline CEA score as the covariate.
- The mean difference between PSA scores at Week 4 will be analyzed using an analysis of variance model (ANOVA) with factors for treatment group and investigator.

Does the Division agree with the primary endpoints?

Response:

Regarding the primary efficacy assessments:

As was stated at the Guidance Meeting on October 31, 2007, "To demonstrate efficacy, the sponsor will need a co-primary endpoint composed of both an investigator assessment and a subject self-assessment (for erythema). Ideally, the scales for these assessments will have category descriptors that are clearly defined, mutually exclusive, and clinically meaningful, and the scales will have been validated."

To be clinically meaningful, the category descriptors should be non-comparative; the category descriptors for grades 3 and 4 of the Physician Global Assessment Scale for Erythema (PGA-E; referenced as Clinician's Erythema Assessment Scale in the briefing document) are relative to grades 2 and 3. The sponsor may consider using photographic examples of each grade for investigator training. Submit investigator training materials to the IND and NDA.

Meeting Discussion

The sponsor indicated that they would remove the comparative language from the descriptors and would consider use of photographs as suggested.

The Patient Self Assessment Scale (PSA) is a dynamic scale with nine categories. To avoid recall bias, assessment scales should be static. It is important that assessment scales are clinically meaningful. Generally, this means that the scale will contain a limited number of categories with category descriptors that are clearly described, non-comparative, and mutually exclusive, and include a “clear” category that represents true absence of disease.

Meeting Discussion

The sponsor asked the Agency their thoughts on using a visual analog scale.

The Agency stated that the patient and investigator scales should be comparable and that the success seen should be clinically meaningful. An internal discussion would need to take place in reference to a VAS before sharing thoughts on that specific scale. A proposal from the sponsor would be needed for the basis of the discussion.

Regarding the primary efficacy endpoints:

As was stated at the Guidance Meeting on October 31, 2007, “Since the sponsor’s product has a transient (non-durable) effect on erythema, the primary endpoint should reflect the assessment over the whole course of the trial. The sponsor might use a repeated measurement approach to capture a clinically relevant treatment effect over the course of the trial. The sponsor should propose to the Division what they consider to be a clinically meaningful difference at each time point to be included in the repeated measurement to evaluate the treatment effect over the course of the trial.”

1. The Patient Self Assessment (PSA) scale should be a static assessment that does not rely on the subjects’ recollection or baseline disease severity. The PSA scale should correspond with the Physician Global Assessment – Erythema (PGA-E).
2. Measurements at each visit should be dichotomized based on whether a subject achieved a clinically meaningful treatment effect. A subject will be classified as a success at a certain visit if the subject achieved successes in both of the co-primary endpoints. Thus, the primary efficacy endpoint will be based on the repeated measurements.
3. For enrollment in the trial, a subject should have a minimum score (3) on the Physician’s Global Assessment – Erythema (PGA-E) and Patient’s Self Assessment (PGA) at baseline.

Meeting Discussion

The sponsor’s preference is to use the IGA and the PSA as a co-primary endpoint each to stand alone.

The Agency emphasized the need to use the two scales simultaneously to define success as both scales are highly correlated.

The Agency indicated that the two measures are expected to be highly correlated. For success to be clinically meaningful, results should be concordant.

Additional comments:

After the sponsor completes development of acceptable primary efficacy measures, the sponsor should conduct an appropriate dose ranging study to get treatment effect estimates based on the endpoints recommended by the division. The sponsor's proposed sample size calculate is inadequate for the following reasons:

- a. The proposed concentration for the phase 3 trials (^{(b) (4)}%) was not investigated in the phase 2 trial; and
- b. The primary endpoint used in the sample size calculation is only one component of the endpoint recommended by the Division; and
- c. The dosing frequency is not the same in the phase 2 studies and the proposed phase 3 trials.

As was stated at the Guidance Meeting on October 31, 2007, "Approval for this indication, which represents a manifestation of a disease process and not the disease itself, will necessitate demonstration of success for an acceptable co-primary endpoint (for the manifestation) as well as the absence of exacerbation or progression of the disease itself." At the same meeting (October 31, 2007), it was further stated, "It will be important to assess global disease severity (not just erythema) to ensure that treatment of erythema does not result in exacerbation of other manifestations of the disease. This assessment should include both an investigator global assessment (for overall disease, not just erythema, and incorporating such elements as papules/pustules and nodules) as well as lesion counts." The protocol does not include an Investigator Global Assessment for overall disease severity or lesion counts. Please address this.

Meeting Discussion

The sponsor will add an IGA for overall disease severity (in addition to lesion counts) as a safety assessment.

We note that you intend to enroll subjects with up to 10 inflammatory lesions. As was stated at the Guidance meeting on October 31, 2007, "It is not clear how you intend to differentiate between reduction of the transient perilesional erythema of inflammatory (papulopustular) lesions versus the reduction of the nontransient erythema not associated with papulopustular lesions. The clinical utility of transient reduction of the perilesional erythema of the inflammatory lesions in subjects with papulopustular rosacea, without treating the inflammatory papulopustular lesions themselves, is not clear." Please address this.

Meeting Discussion

The sponsor does not plan to seek an indication for perilesional erythema. They are seeking an indication for nontransient erythema, and not the treatment of papules and pustules.

Question 3:

Does the Division wish to provide comment on the long-term safety of COL-118?

Response:

Safety evaluation should include evaluation of local effects such as atrophy. Assessment of global disease severity is important to ensure that the treatment of erythema does not result in exacerbation of other manifestation of the disease. Provide rationale for excluding pregnant subjects from the study.

Question 4:

Does the Division agree with the plans for including the two 3-month, safety and efficacy studies in the NDA followed by an interim analysis of the 2 year safety study as a 120 day safety update?

Response:

No, we do not agree. The safety database should be complete at time of NDA submission.

Additional comments:

The Division recommends the sponsor to conduct sensitivity analysis to ensure that the efficacy is not driven by extreme center if the treatment by center interaction term is statistically significant at the $\alpha=0.10$ level.

The sponsor's proposed to not impute missing data as a sensitivity analysis. It should be noted that this available case method is subject to bias and is only valid when the missingness is Missing Completely at Random (MCAR). Therefore might not be that useful as a sensitivity analysis. The Division recommends the sponsor to pre-specify sensitivity analyses in the protocol that take non-random missingness into account.

The sponsor defined the ITT population as patients who were randomized and received at least one application of study medication. The ITT population should include all randomized subjects, regardless of whether they have received study medication.

The sponsor stated that in the case that the residuals from the ANOVA model are non-normal, they will perform a supplementary non-parametric analysis. If the data does not meet the model assumptions, the non-parametric analysis should be considered as the primary analysis.



Safety evaluation should include monitoring of intraocular pressure (Guidance Meeting, October 31, 2007)

Prior to demonstration of either the absence of an effect on cardiac repolarization in a thorough QT/QTc study or the absence of systemic exposure in a PK study conducted under maximal use conditions in diseased subjects, all subjects should have ECGs at appropriate intervals to ensure subject safety. The sponsor is referred the Guidance for Industry ICH E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Anti-arrhythmic Drugs. (PIND Meeting, August 9, 2006; Guidance Meeting, October 31, 2007)

Provide methods to ensure the blind. (Guidance Meeting, October 31, 2007)

Please provide the rationale for selection of a concentration ((b) (4) % COL 118) that was not studied in phase 2 study (Guidance Meeting, October 31, 2007). Please clarify the dosing regimen for the phase 3 trials (qd vs BID), and the rationale for selection of a dosing regimen in phase 3 that was not evaluated in the phase 2 study.

Please provide rationale for excluding pregnant women from phase 3 clinical trials (Guidance Meeting, October 31, 2007).

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. 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. You are 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 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.
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.
10. For a 505(b)(2) application, you must clearly identify those portions of the application that rely on information you do not own or to which you do not have a right of reference.
11. A 505(b)(2) application that relies upon the Agency's previous finding of safety or efficacy for a listed drug must specifically identify any and all listed drugs by established name, proprietary name, dosage form, strength, route of administration, name of the listed drug's sponsor and the application number.
12. A 505(b)(2) application relying upon literature must clearly identify the listed drug(s) on which the studies were conducted (if any).
13. For a 505(b)(2) application you must provide a patent certification or statement as required under section 505(b)(2) of the Act with respect to any relevant patents that claim the listed drug and that claim any other drugs on which the investigations relied on by you for approval of the application were conducted, or that claim a use for the listed or other drug (21 CFR 314.54(a)(1)(vi)). -- (Listed in the Orange Book)
 - Patent certification should specify the exact patent number(s), and the exact name of the listed drug or other drug even if all relevant patents have expired.
 - You must also submit a relative bioavailability study comparing the proposed product to the listed drug(s) (if any).
14. Key Issue regarding the requirement for appropriate patent certification: Due to legislation contained in the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA), if during the review of an NDA filed under 505(b)(2), either the applicant decides to refer to a different product than that/those identified in the original application, or the Agency discovers that the applicant did not appropriately certify to the patent(s) of the products referenced in the original application, then the applicant would be required to withdraw and resubmit the application as a new original NDA, with the appropriate Patent Certifications included, potentially requiring a new User Fee.
15. Before submitting the NDA, the guidance recommends that you submit a plan to the reviewing Division that specifically identifies the types of bridging studies that will be conducted. You should also identify those components of the application for which you expect to rely on FDA's finding of safety and effectiveness of a previously approved drug product. The Division will critique the plan and provide guidance.
16. The review of this plan will be completed around reviewing Division's deadlines that may take higher priority; therefore, we encourage you to submit such a plan well in advance of the NDA submission, to provide adequate time for the reviewer to evaluate the proposal and resolve any potential concerns that may result in a filing issue or delay in the review process.
17. If the only literature that you submit is within the public domain and/or if you have a right of reference to the studies and the data required to support them, you may be able to submit a 505(b)(1) application.

18. If portions of the application rely upon studies that you do not have right of reference to or are not within the public domain, you must submit a 505(b)(2) application. Typically not all studies reported in the literature are supported by data that exists within the public domain. Many studies in the literature are supported by proprietary data.

Minutes Preparer: _____
Tamika White/Regulatory Project Manager, DDDP, HFD-540

Chair Concurrence: _____
Susan J. Walker, M.D./Division Director, DDDP, HFD-540

Linked Applications

Sponsor Name

Drug Name

IND 74841

COLLAGENEX
PHARMACEUTICALS
INC

COL 118(BRIMONIDINE TARTRATE

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

/s/

SUSAN J WALKER
03/13/2008



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 74,841

Collagenex Pharmaceuticals, Inc
Attention: Christopher Powala, Vice President
Drug Development and Regulatory Affairs
41 University Drive, Suite 200
Newtown, PA 18940

Dear Mr. Powala:

Please refer to your Pre-Investigational New Drug Application (PIND) file for COL-118 (brimonidine tartrate) topical (b) (4) gel for the treatment of erythema (b) (4) in adult patients with rosacea.

We also refer to the meeting between representatives of your firm and the FDA on August 9, 2006. The purpose of the meeting was to provide feedback on the sponsor's development plan for COL-118 (brimonidine tartrate) topical (b) (4) gel.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

Sincerely,

{See appended electronic signature page}

Stanka Kukich, M.D.
Deputy Division 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: August 9, 2006 **Time:** 10:00 A.M.
Location: WO 1309 **Meeting ID:** 19488
Topic: PIND 74,841, COL-118 (brimonidine tartrate) topical
(b) (4) gel for the treatment of erythema (b) (4)
in adult patients with rosacea.
Subject: Pre-IND meeting
Regulatory Path: 505(b)(2)
RLD: Alphagan®
Sponsor: Collagenex Pharmaceuticals, Inc.
Meeting Chair: Stanka Kukich, M.D./Deputy Division Director, DDDP
Meeting Recorder: Melinda Bauerlien, M.S./Regulatory Project Manager, DDDP

FDA Attendees:

Stanka Kukich, M.D./Deputy Division Director, DDDP
Nancy Boocker/Director, DRP1, ORP
Jill Lindstrom, M.D./Team Leader, Clinical, Dermatology, DDDP
Patricia Brown, M.D./Clinical Reviewer, DDDP
Paul Brown, Ph.D./Supervisor, Pharmacology, DDDP
Kumar Mainigi, Ph.D./Pharmacology Reviewer, DDDP
Shulin Ding, Ph.D./Pharmaceutical Assessment Lead
Mat Soukup, Ph.D./Biostatistician, DBIII
Dennis Bashaw, Pharm.D./Director, DCPIII
Suliman Al-Fayoumi, Ph.D./ Clinical Pharmacology and Biopharmaceutics Reviewer, DCPIII
Donald Hare, Pharm.D./Special Assistant to the Director, OGD
Melinda Bauerlien, M.S./Regulatory Project Manager, DDDP, HFD-540

Sponsor Attendees:

Collagenex, Pharmaceuticals, Inc.

Christopher Powala/Vice President, Drug Development and Regulatory Affairs
Mark Bradshaw, Ph.D./Biostatician
Bill Groff/Director of Manufacturing
(b) (4)
Jean Siegel/Consultant

Phil Freidenreich/Senior Director, Quality Assurance and Compliance

Purpose:

To provide general guidance on the content and format of the proposed new Investigational New Drug Application under 21CFR 312. The pre-meeting briefing document (submitted July 7, 2006) provides background and questions for discussion. The sponsor requests input from the Agency on their development plan.

Chemistry, Manufacturing and Controls:

Sponsor's Question 3:

The sponsor will manufacture (b) (4) a gel (b) (4) (at a single strength) for testing in patients. Each formulation will vary in composition of the inactive ingredients and/or manufacturing process. All inactive ingredients will be GRAS and will have been FDA approved in other pharmaceutical products. The formulations will initially be applied in 50 µl quantities in order to determine in a difference in tolerability, irritancy and pharmacodynamic profile of effect can be detected. The IND Application will include 1 month stability data for each formulation at 25°C/60% RH and 40°C/75% RH to support the clinical use of the product. Stability will be on going through the duration of the clinical trial or longer.

Does the Division agree with this approach?

Agency's Response:

The response is deferred to medical reviewer concerning the appropriateness of the clinical approach. In terms of stability approach, your proposal is acceptable assuming that the stability studies will be done in the jars with screwed caps.

Sponsor's Question 4:

Based on initial testing, up to two formulations of gel (b) (4) will be carried forward with multiple strengths to be tested clinically. The sponsor will conduct stability testing at 25°C/60% RH and 40°C/75% RH.

Does the Division find this acceptable?

Agency's Response:

It is acceptable. If you don't plan to conduct stability studies for every drug strength, make sure that you apply a proper bracketing strategy and cover the lowest and highest strengths for each formulation.

Sponsor's Question 5:

Once a final formulation and strength is chosen, it is planned to develop two primary packaging materials, i.e., a standard 30 gram tube and a unit dose container with applicator sponge (trade named

(b) (4). Given that the variance in application will be higher using a tube, clinical trials will primarily use this presentation.

Does the Division find this acceptable?

Agency's Response:

The sponsor will need to provide information about total exposure and variability for each packaging system. Sufficient study of the exposure to study drug for each packaging system will be necessary. The sponsor is invited to discuss this at the appropriate time in development. Please provide samples for each packaging configuration for evaluation.

The sponsor provided packaging configuration samples for the unit dose packaging.

Pharmacology/Toxicology:

Sponsor's Questions 6 and 7:

The pharmacology and toxicology of brimonidine is well characterized. Brimonidine tartrate is FDA approved as an ophthalmic solution for the treatment of open-angle glaucoma (See Attachment #1 for Approved Package Insert). The sponsor does not plan to conduct any toxicology studies and will rely on the approved label text for toxicology.

Does the Division agree?

Because the pharmacology of brimonidine is well understood, the sponsor will provide a summary of published literature to justify its use in human clinical trials and to support an NDA.

Does the Division agree?

Agency's Response:

If the sponsor uses the marketed formulation for initial studies then single dose protocols may be considered reasonably safe although a final safety decision will be made under the IND.

The sponsor stated that they felt that the safety of the drug product was well established. However, the Agency noted that the dermal safety of the sponsor's yet to-be-selected topical product would still need to be assessed regardless of previous safety assessments of the drug substance.

Repeat dose topical clinical studies should be supported by adequate repeat dose nonclinical studies with the clinical formulation (See ICH M3 for guidance on the recommended timing and duration.) These should be GLP-compliant with complete toxicity evaluations and toxicokinetics. Dermal sensitization studies of the clinical formulations to be used are also recommended prior to human use. Since the product will be used on the face, the ocular irritation potential of the clinical formulations should be assessed.

The sponsor cannot refer to materials submitted to other INDs without permission from the holder of that IND.

The sponsor intends to submit an NDA under section 505(b)(2) of the FD&C Act. A 505(b)(2) NDA may refer to the Agency's finding of safety for an approved drug product only if an adequate clinical bridge is established to that particular approved product. In the case of brimonidine tartrate, the Agency's finding of safety was for the use of small amounts of drug in the eye. Therefore, the ophthalmic and oral studies are not sufficient to support the safety of dermal preparations to be used in a chronic condition. Additional nonclinical data from studies such as those noted above are recommended even if an adequate clinical bridge can be established.

If an adequate clinical bridge is not established to an approved drug product then an NDA should be supported by complete nonclinical information. In a 505(b)(1) NDA this information should be from studies conducted by or for the sponsor or for which the sponsor has right to refer. In a 505(b)(2) NDA without a clinical bridge to an approved product, the nonclinical information can be from the same sources as noted above for a 505(b)(1) NDA and from literature information for which the sponsor does not have the right to the underlying data, provided that this literature is considered adequate and complete.

The Agency noted that the final formulation was not yet established and so it could not comment on the safety of excipients. The safety of the excipients should be adequately supported as per the recommendations in the Guidance for Industry entitled: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients.

Clinical Pharmacology and Biopharmaceutics:

Sponsor's Question 10:

It is anticipated that there will be no meaningful systemic absorption from brimonidine applied topically to the face. The sponsor intends to evaluate systemic exposure during full face Phase 2 testing. Should the sponsor fail to detect systemic levels of brimonidine, it would consider Biopharmaceutics testing complete.

Does the Division agree with this approach?

Agency's Response:

It has been the Agency's policy to request that a maximal usage study be undertaken in a suitable number of subjects with the dermatological disease of interest at the upper range of severity as anticipated in both your clinical trials and proposed labeling. Such a trial would attempt to maximize the potential for drug absorption to occur by incorporation of the following design elements:

- a) Frequency of dosing
- b) Duration of dosing
- c) Use of highest proposed strength
- d) Total involved surface area to be treated at one time
- e) Amount applied per square centimeter

f) Method of application/site preparation

It is important to note that patients participating in this study should have maximum diseased surface area as percutaneous absorption can differ between healthy skin and diseased skin.

The trial itself could be a stand alone trial in phase 2 or could be a sub-group of subjects in a larger phase 3 trial. Either approach is acceptable and has been used successfully by other sponsors.

Addendum

The aforementioned pk study should include at least 18-24 completers. The study should be multiple dose in nature and should include a comparator arm (ie. the ophthalmic product) to provide a direct comparison of the levels between the two routes of administration and formulation. As part of a 505(b)(2) program, provided that the levels produced by your product are lower than those seen with the ophthalmic product, this finding could be part of the "bridge" to support the systemic safety of your product.

Clinical:

Sponsor's Question 1:

COL-118 will be developed with an intent to file an NDA pursuant to **section 505(b)(2)** of the Food, Drug and Cosmetic Act(Act). However, should the Division require additional toxicology, the NDA would be filed pursuant to section 505 (b)(1) of the Act.

Does the Division agree with this approach?

Agency's Response:

You are considering the submission of an application described in section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. This regulatory pathway to approval is described at 21 C.F.R. 314.54, and in the 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/cder/guidance/guidance.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the agency's interpretation of this statutory provision. See Dockets 2001P-0323, 2002P-0447, and 2003P-0408.

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for a listed drug, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug. In this case, you should establish a "clinical bridge" between your proposed drug product and your listed drug to demonstrate that reliance is appropriate. If you intend to rely on literature or other studies that you have no right of reference to but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

The sponsor agreed.

Sponsor's Question 2:

Should the Sponsor file an NDA pursuant to section 505 (b)(2) of the Act and should the NDA contain data from clinical investigations (other than bioavailability studies) that were essential for approval, it is the Sponsor's understanding that it would be granted a 3 year period of exclusivity. Given this exclusivity, the Agency will not make effective the approval of any product containing brimonidine tartrate for the indication being sought herewith, regardless as to whether an applicant, other than CollaGenex, filed an application pursuant to section 505 (b) or 505 (j) of the Act.

Does the Division agree that if the NDA for COL-118 was filed pursuant to section 505 (b)(2) of the Act, it would qualify for an exclusivity period of 3 years?

Agency's Response:

The determination of whether an NDA is entitled to exclusivity is not made until the NDA is approved by the Agency. If you choose to file an NDA, pursuant to section 505(b)(2), which contains reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by you that were essential to approval of the application, you would be eligible for 3-year exclusivity. For additional information on the scope of 3-year exclusivity, see sections 505(c)(3)(E)(iii)-(iv) and 505(j)(5)(F)(iii)-(iv) of the Federal Food, Drug, and Cosmetic Act, and FDA's regulations at 21 C.F.R. 314.108. Please note that approval of a 505(b)(1) application would not be delayed by 3-year exclusivity.

The sponsor would be eligible for Waxman-Hatch exclusivity if they fulfill the requirements by submission of clinical efficacy and safety data from 2 well-controlled clinical trials.

The sponsor agreed.

Sponsor's Question #8:

The Sponsor intends to conduct the following clinical development program:

Protocol COL118-ROSE-101: Apply 50µl of a serial dilution of a commercially available ophthalmic solution of brimonidine tartrate to 1 cm² areas of affected skin (malar region) to approximate the dose response-relationship (DRR). Single application of various dilutions will be applied to 6 areas per patient (N=10 patients). Chromameter readings at(sic) will be obtained at various intervals. Objective: determine a strength that is ~75% maximally effective. A draft of this protocol can be found in Attachment # 2.

Protocol COL118-ROSE-102: Apply 50µl of up to 6 different formulations that contain brimonidine tartrate at the ~75% maximally effective strength, as determined in Study COL118-ROSE-101, to 1 cm² areas of affected skin to approximate the pharmacodynamic profile (PD). Single application, 6 areas per patient (N = 10 patients). Chromameter readings will be obtained at various intervals. Objective: determine the impact of formulation on the PD profile. A draft of this protocol can be found in attachment # 3.

Protocol COL118-ROSE-201: Apply three different strengths plus vehicle of two different formulations to the affected areas in the face to establish the DRR and PD profile. Patients will be dosed for 4 weeks and up to twice daily applications; eight groups, parallel design. Assessment of PD profile and brimonidine plasma levels on Day 0, 14, and 28 (N = 96 patients). Objective: select the final formulation and strength for phase 3 testing. A draft of this protocol can be found in Attachment # 4.

The sponsor believes that the conduct of the above three trials will yield the appropriate data to determine and (sic) appropriate dose and formulation for use in Phase 3 testing.

Does the Division agree with the overall Phase 1-2 clinical approach?

Agency's Response:

This approach is not sufficient. In early development (Phases 1/2) it is important to study dose ranging in order to select a dose that maximizes safety and efficacy. It is also important to study PK parameters, refine endpoints, and explore treatment effects for powering Phase 3 studies.

Topical safety studies:

The sponsor should conduct dermal safety studies using the final to-be-marketed drug products. Generally, the required topical safety studies are cumulative irritancy (not less than 30 evaluable subjects), contact sensitization (not less than 200 evaluable subjects), photoallergenicity (not less than 50 evaluable subjects), and phototoxicity (not less than 30 evaluable subjects). These studies should be conducted with the final to-be-marketed formulation and are usually conducted in parallel with phase 3 studies. However, if Phase 1/2 studies should reveal an irritancy signal and the product is to be labeled as an irritant, cumulative irritancy testing may not be needed. Phototoxicity and photoallergenicity studies may be waived by the Agency if there is no absorption in the UVB, UVA, or visible light spectrum, or if the product will be labeled only for use under an opaque dressing.

The sponsor agreed.

Dose ranging:

The sponsor is exploring a variety of doses in protocols COL118-ROSE-101 and COL118-ROSE-210. Dose ranging studies should investigate safety and efficacy at ranges in concentration, frequency, and duration of therapy which bracket response and allow determination of the formulation most likely to succeed in Phase 3.

The sponsor agreed.

Sponsor's drug/indication:

The indication being sought appears to be reduction of rosacea related erythema or alternatively erythema (b) (4) in adult patients with rosacea. Please clarify the indication. Please clarify how an indication for rosacea related erythema (b) (4) relates to the broader context of rosacea treatment as a whole. What type(s) of rosacea will be studied? What type of rosacea patients will be studied? (b) (4)

The indication should be one that is clinically relevant.

The sponsor indicated that the exact indication remains to be determined. They are considering erythema (b) (4) in patients with rosacea.

The Division responded that this indication may only be appropriate if patients with all types of rosacea are enrolled. If the sponsor wishes to study a more narrow population, the narrow population will need to be reflected in the indication. The indication needs to be a clinically recognized entity. It will be important to ascertain that other types of lesions, e.g. (b) (4) (b) (4) were not adversely affected.

The sponsor may need to evaluate different skin types since the erythema of rosacea may be appreciated differently in certain skin types.

Protocols Submitted:

Efficacy evaluation: The primary efficacy parameter is stated to be change in Minolta Chromameter measurement from pre-dose to 2 hours post-dose. The secondary efficacy parameter is stated to be the duration of change in erythema as measured by Chromameter to the point in time where the effect is lost (as judged visually). While a change in Chromameter measurement may be acceptable in early phase studies, an endpoint that is clinically relevant and can be translated into labeling is needed. Such an endpoint will be needed for both Phase 3 studies and for those Phase 2 studies of treatment effect used to power Phase 3 studies. It is noted that the sponsor is evaluating patients at baseline with the Clinician's Erythema Assessment Score and using this scale for study entry. Further use of this scale in these studies is not mentioned.

The Division will be willing to evaluate a scale as proposed by the applicant for measuring clinical success.

Safety:

1) Due to application proximity to the eyes, please consider the monitoring of ocular pressure in early phase development.

This may be performed on a subset of patients.

2) Until a thorough QT/QTc study is performed (per ICH Guidance E14), ECG monitoring will be needed. This should be performed at baseline, at mid-point when drug concentration has reached steady state, and at the end of the study.

The sponsor questioned whether ECG monitoring would be necessary since this drug would be applied topically. All applicants need to satisfy the safety data needs of ICH E14, regardless of dosage form. Systemic exposure data for the drug needs to be evaluated.

Sponsor's Question 9:

“Prior to CollaGenex taking Sponsorship of this product, a small clinical trial in 9 patients was conducted. Attachment # 5 contains before and after photographs of patients. One observation is that the product works quickly and effectively. This said, it would be near impossible to maintain the study blind once the product is evaluated in large Phase 3 trials.

Would the Division consider open-label studies for approval?”

Agency's Response:

Double blind studies are necessary to assure that there is no bias in assessment of safety and efficacy. A double blind design has been proposed by the sponsor for protocol COL-118-ROSE-201. The sponsor is requested to propose methods to ensure the blind.

This issue will be discussed further at the appropriate stage in drug development. Many factors are currently unknown. Blinded studies are preferred.

The sponsor is referred to the ICHE1a guidance in terms of numbers of patients needed on drug product for long-term safety and to the ICHE5 guidance concerning a good demographic balance of patients.

Biostatistics:

The sponsor intends to conduct 3 trials (Protocols: ROSE-101, Rose -102 and Rose-201) for which "the sponsor believes that the conduct of the above three trials will yield the appropriate data to determine and appropriate dose and formulation for use in Phase 3 testing". Then the sponsor raised the following question:

Sponsor's Question 8:

The sponsor believes that the conduct of the above three trials will yield the appropriate data to determine and(sic) appropriate dose and formulation for use in Phase 3 testing.

Does the Division agree with the overall Phase 1-2 clinical approach?

Agency's Response:

As the proposed design for studies Roase-101 and Rose 102 involves several concentrations to different areas on the malar region of the face might provide an overall safety evaluation of the drug product; which might be acceptable in the early clinical development program (see clinical comments), however the proposed design is not adequate for comparative evaluation of the safety and efficacy of different drug concentrations. Thus the sponsor should consider other future Phase 2 dose ranging studies to select the appropriate dose for their final clinical development program.

The proposed primary endpoint in each of these studies is "Change in Minolta Chromameter measurement from pre-dose to 2 hours post-dose"; and the secondary efficacy is the duration of change in erythema as measured by chromameter to the point in time where the effect is lost (as judged visually). It should be noted that the protocols did not specify the range of change in Minolta chromameter measurements or the magnitude of change which would be considered meaningful. Further, it is not clear whether the proposed measurement is clinically appropriate for evaluating disease improvement. While for early development the sponsor might investigate different endpoints for getting and idea about efficacy, it should be noted that for regulatory action based on Phase 3 trials efficacy should be established based on clinically relevant endpoints agreed upon with the Division. By getting estimate of treatment effect for the selected dose for such primary endpoint and using such

estimate for powering future Phase 3 trials the sponsor reduces their chances of under powering such trials.

Under the title Statistical Considerations, each of the proposed studies included a general discussion about the statistical analyses. It should be noted that for early development including dose-ranging studies no formal statistical testing is required. Further, at this stage, it would be difficult to comment on appropriateness of general statistical methodology when the endpoint is not yet defined.

Drug development is a sequential process, the sponsor is encouraged to conduct their early development program sequentially, and benefit from the experience and data gained from a certain stage to plan and conduct next stage in the clinical development program.

Administrative Comments

1. 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).
2. 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 an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.
3. 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 Phase 2 trials do not necessarily constitute commitments that can be extrapolated to Phase 3 trials.
4. Your pre-IND has been assigned # 74,841. Please reference this number on all submissions and correspondence. **Please note, studies in humans may not be conducted under this PIND. Before you may conduct studies in humans, you must submit an Investigational New Drug Application (IND, see 21 CFR Part 312).**
5. When you submit your Investigational New Drug Application, please provide 5 copies.

Minutes Preparer: _____
Melinda Bauerlien, M.S./Regulatory Project Manager, DDDP

Chair Concurrence: _____
Stanka Kukich, M.D./Deputy Division Director, DDDP

**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
9/6/2006 09:15:13 AM