

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204708Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

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

Date: August 21, 2013

From: Hitesh Shroff, Ph.D.
Senior CMC Reviewer
New Drug Quality Assessment Division II
ONDQA

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
New Drug Quality Assessment Division II
ONDQA

To: CMC Review #1 of NDA 204708

Subject: Final Recommendation

The CMC review #1 has noted the following pending issues:

- Label/labeling issues were not resolved.

On August 21, 2013, the final label and labeling were submitted and they are revised satisfactorily from the ONDQA perspective (see the **Attachment**).

Recommendation:

This NDA is **now** recommended for approval from the ONDQA perspective, with an expiration dating period of 24 months.

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

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/s/

HITESH N SHROFF
08/21/2013

MOO JHONG RHEE
08/21/2013
Chief, Branch IV

NDA 204708**Mirvaso (brimonidine) topical gel
0.33%****Galderma Research and Development, Inc.****Hitesh Shroff, Ph.D.**

Review Chemist

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch IV****CMC Review of NDA 204708
For the Division Dermatology and Dental Products
(HFD-540)**

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Chemistry Review Data Sheet

1. NDA 204708
2. REVIEW:#1
3. REVIEW DATE: 21-Jun-2013
4. REVIEWER: Hitesh Shroff, Ph.D.
5. PREVIOUS DOCUMENTS: N/A
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	25-Oct-2012
Amendment	20-Nov-2012
Amendment	05-Feb-2013
Amendment	16-May-2013

1. NAME & ADDRESS OF APPLICANT

Name: Galderma Research and Development, Inc.
Address: 5 Cedar Brook Drive
Cranbury, NJ 08512

Representative: Elaine Clark
Senior Director US Regulatory Submissions
14501 North Freeway
Fort Worth, TX 76177

Telephone: 682-831-6915
Email: elaine.clark@galderma.com

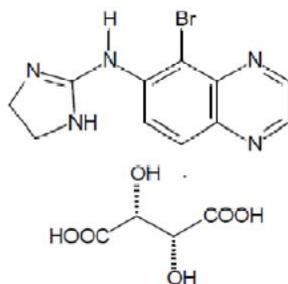
8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Mirvaso
- b) Non-Proprietary Name (USAN): brimonidine tartrate
- b) Code Name/# (ONDQA only): None
- c) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: α 2-Adrenergic agonist

11. DOSAGE FORM: Gel
12. STRENGTH/POTENCY: Brimonidine 0.33 % (5 mg/g brimonidine tartrate)
13. ROUTE OF ADMINISTRATION: Topical
14. Rx/OTC DISPENSED: X Rx ___ OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
___ SPOTS product – Form Completed
X Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOLECULAR WEIGHT:



brimonidine tartrate

USAN Name:	Brimonidine tartrate
Chemical name:	5-Bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine L-tartrate 5-Bromo-6-(2-imidazol-2-ylamino) quinoxaline tartrate
CAS numbers:	Base: [59803-98-4] Tartrate: [70359-46-5]
Molecular Formula:	C ₁₁ H ₁₀ BrN ₅ • C ₄ H ₆ O ₆
Molecular Weight:	442.2 ^(b) / ₍₄₎ g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	09-11-2012	Richard Chang
	II		3	Adequate	05-23-2013	Hitesh Shroff	
	III		4				
	III		4				

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	27-Dec-2012	Marissa Stock
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMEPA	N/A		
EA	Claim for categorical exclusion granted	Oct-26-2012	Hitesh Shroff, CMC
Microbiology	N/A		

The Chemistry Review for NDA 204708

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product.

The Office of Compliance has issued an "Acceptable" recommendation for the facilities involved in this application.

The label/labeling issues are still *not* satisfactorily resolved.

Therefore, from the ONDQA perspective, this NDA is *not* ready to recommend for approval in its present form per 21 CFR 314.125(b)(6), until the pending issues are satisfactorily resolved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

No recommendations at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

(1) Drug Substance

Mirvaso topical gel contains 5 mg of active ingredient, brimonidine tartrate. Brimonidine tartrate is a white to slightly yellow powder. It is manufactured by (b)(4). The detailed CMC related information for the drug substance is provided in DMF (b)(4) and DMF (b)(4). The applicant provided letters of authorization to reference both DMFs in connection with NDA 204708. The DMF (b)(4) and DMF (b)(4) were reviewed on 09-11-2012 and 05-23-2013 respectively. Both DMFs were found to be adequate.

(2) Drug Product

Mirvaso (brimonidine) topical gel, 0.33% is a white to light yellow, opaque gel. It is supplied in 30 g and 45 g laminated tubes with child-resistant caps to protect it from light and moisture. Each gram of Mirvaso topical gel contains 5 mg of brimonidine tartrate. The inactive ingredients of the drug products are carbomer homopolymer type

Executive Summary Section

B, glycerin, methylparaben, phenoxyethanol, propylene glycol, purified water, sodium hydroxide and titanium dioxide.

The manufacturing of Mirvaso topical gel is performed using (b) (4) batches containing approximately (b) (4) of gel were manufactured at (b) (4). Three primary stability (b) (4).

The proposed release specification of the finished product include appearance, identification, assay of the active ingredient and preservatives, pH, impurities, and microbial limits. The proposed specification are deemed adequate to assure the identity, strength, purity, and quality of the drug product.

Based on the stability data from three production scale batches of drug product at long term (36 months) and accelerated (6 months) conditions, the proposed 24 months expiration dating period, when stored at room temperature, is granted.

B. Description of How the Drug Product is Intended to be Used

Mirvaso topical gel is a selective α -2 adrenergic agonist indicated for the treatment of facial erythema of rosacea in adults. A typical dosage is a small pea-size amount to each of five areas of the face applied once daily. Mirvaso topical gel is supplied in 30 g and 45 g tubes with child resistant caps.

C. Basis for Not-Approval Recommendation

21 CFR 314.125 (b)(6)

- The label/labeling issues are not finalized (see the **List of Deficiencies**, p. 78)

III. Administrative**A. Reviewer's Signature**

Hitesh Shroff, Ph.D./ 21-Jun-2013

B. Endorsement Block

Moo-Jhong Rhee, Ph.D., Branch Chief, Branch IV, Division 2

C. CC Block

Shulin Ding, Ph.D.

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/s/

HITESH N SHROFF
06/21/2013

MOO JHONG RHEE
06/21/2013
Chief, Branch IV



CHEMISTRY REVIEW



Chemistry Assessment Section

IV. Attachment

EES Report

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application:	NDA 204708/000	Sponsor:	GALDERMA R AND D
Org. Code:	540		5 CEDAR BROOK DR STE 1
Priority:	3		CRANBURY, NJ 08512
Stamp Date:	25-OCT-2012	Brand Name:	COL-118 (Brimonidine Tartrate)Topical Ge
PDUFA Date:	25-AUG-2013	Estab. Name:	
Action Goal:		Generic Name:	COL-118 (Brimonidine Tartrate)Topical Ge
District Goal:	26-JUN-2013	Product Number; Dosage Form; Ingredient; Strengths	001; GEL; BRIMONIDINE TARTRATE; .5%

FDA Contacts:	H. SHROFF	Prod Qual Reviewer		3017962116
	C. TRAN-ZWANETZ	Product Quality PM	(HFD-800)	3017963877
	D. WILLIAMS	Regulatory Project Mgr	(HFD-540)	3017965376
	S. DING	Team Leader		3017961349

Overall Recommendation: ACCEPTABLE or (b) (4) by STOCKM
 PENDING on 17-DEC-2012 by EES_PROD
 PENDING on 14-NOV-2012 by EES_PROD

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)

DMF No: [REDACTED] **AADA:**

Responsibilities: DRUG SUBSTANCE LABELER
 DRUG SUBSTANCE MANUFACTURER
 DRUG SUBSTANCE PACKAGER
 DRUG SUBSTANCE RELEASE TESTER
 DRUG SUBSTANCE STABILITY TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 27-DEC-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION



CHEMISTRY REVIEW



Chemistry Assessment Section

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Establishment: CFN: FEI: 3003671557
 GALDERMA PRODUCTION CANADA, INC.
 19400 ROUTE TRANSCANADIENNE
 BAIE-D'URFE, QUEBEC, CANADA

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
 FINISHED DOSAGE MANUFACTURER
 FINISHED DOSAGE OTHER TESTER
 FINISHED DOSAGE PACKAGER
 FINISHED DOSAGE RELEASE TESTER
 FINISHED DOSAGE STABILITY TESTER

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-DEC-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE LABELER
 DRUG SUBSTANCE MANUFACTURER
 DRUG SUBSTANCE PACKAGER
 DRUG SUBSTANCE RELEASE TESTER
 DRUG SUBSTANCE STABILITY TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 03-DEC-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Initial Quality Assessment
Branch IV
Division of New Drug Quality Assessment II

OND Division: Division of Dermatology and Dental Products
NDA: 204708
Applicant: Galderma Research and Development , Inc.
Stamp Date: Oct. 26, 2012
PDUFA Date: Aug. 25, 2013
Trademark: Mirvaso®
Established Name: Brimonidine Tartrate
Dosage Form: Gel
Route of Administration: Topical
Indication: Treatment of facial erythema of rosacea

CMC Lead: Shulin Ding

	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Summary and Critical Issues:

A. Summary

Galderma has submitted a 505(b)(2) New Drug Application (NDA) for the prescription use of Mirvaso® (brimonidine tartrate) gel, 0.5% for the topical treatment of facial erythema of rosacea.

The applicant references DMF (b)(4) held by (b)(4), and DMF (b)(4) held by (b)(4) (b)(4) for the CMC information of the proposed drug substance. Letters of authorization from the two DMF holders have been provided. The proposed drug substance manufacturing sites are located in (b)(4). DMF (b)(4) was reviewed very recently but DMF (b)(4) has not been reviewed since Feb. 4, 2008. Both DMFs were deemed adequate to support ophthalmic NDAs by their last CMC reviews.

The proposed drug product is a white to light yellow opaque gel packaged in laminated aluminum tubes equipped with a child-resistance (b)(4) cap. The proposed trade sizes are 30 g and 45 g. (b)(4)

In addition to the active ingredient, the formulation also contains the following excipients: propylene glycol, USP; (b)(4), NF; glycerin, USP; methylparaben, NF; phenoxyethanol, NF; sodium hydroxide, NF; titanium dioxide, USP; and purified water, USP. All excipients are compendial, and none originate from human/animal source.

The to-be-marketed formulation (Table 1) is the same formulation used in Phase 3 clinical trials and registration stability batches. The formulation is prepared (b)(4)

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C. Comments for 74-Day Letter:

1. Submit a representative sample (b)(4) and a low viscosity drug product sample whose viscosity is near the proposed lower limit of the viscosity acceptance criterion (i.e. (b)(4)) for dosage form evaluation.

D. Comments/Recommendation:

The application is acceptable for filing from CMC perspective. The major CMC review issues with this NDA include starting material, drug substance equivalence between two suppliers, drug product container/closure equivalence between child-resistance and non-child-resistance one, and extractables/leachables.

Drug substance manufacturing sites are located in (b)(4). Drug product manufacturing site is located in (b)(4). GMP inspection requests have been submitted.

Shulin Ding, Ph.D.
CMC Lead

Moo-Jhong Rhee, Ph.D.
Chief, Branch IV

NDA Number: 204708 **Supplement Number and Type:** 0000 **Established/Proper Name:** Brimonidine Tartrate, 0.5%

Applicant: Galderma **Letter Date:** Oct. 25, 2012 **Stamp Date:** Oct. 26, 2012

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			n/a

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	x		Categorically exclusion is claimed.

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	x		Also referenced to DMFs (b) (4) for details.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		x	Referenced to DMFs (b) (4).
14.	Does the section contain information regarding the characterization of the DS?	x		Also referenced to DMFs (b) (4).
15.	Does the section contain controls for the DS?	x		Also referenced to DMFs (b) (4).
16.	Has stability data and analysis been provided for the drug substance?	x		Also referenced to DMFs (b) (4).
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	n/a
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	n/a

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		Master Batch Records are submitted in the amendment dated Nov. 30, 2012.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?		x	n/a
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	x		
25.	Does the section contain controls of the final drug product?	x		Regulatory specification is submitted in the amendment dated Nov. 30, 2012.
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	n/a
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	n/a

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	x		Method validation package is submitted in the amendment dated Nov. 30, 2012.

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		x	This is not a sterile product.

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II			(b) (4)	
	II				
	III				
	III				

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			n/a
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	x		See pages 2-3.

{See appended electronic signature page}

Shulin Ding, Ph.D.
 CMC Lead
 Division of New Drug Quality Assessment II
 Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

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

Date

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/s/

SHULIN DING
12/10/2012

MOO JHONG RHEE
12/11/2012
Chief, Branch IV