

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206255Orig1s000**

**CHEMISTRY REVIEW(S)**

# **NDA 206255**

**Soolantra<sup>®</sup> (ivermectin) Cream, 1%**

**Galderma Research and Development, LLC**

**Raymond P. Frankewich, Ph.D.**

**Review Chemist**

**Office of New Drug Quality Assessment  
Division of New Drug Quality Assessment II  
Branch IV**

**CMC REVIEW  
For the Division of Dermatology and Dental Products  
(CDER/ODEIII/DDDP, HFD-540)**

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## CMC Review Data Sheet

# CMC Review Data Sheet

1. NDA 206255
2. REVIEW #: 1
3. REVIEW DATE: 9-October-2014
4. REVIEWER: Raymond P. Frankewich, Ph.D.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	December 24, 2013
Correspondence (C)	
Amendment	February 17, 2014
Amendment	March 31, 2014
Amendment	April 18, 2014
Amendment	April 23, 2014
Amendment	June 27, 2014
Amendment	July 18, 2014
Amendment	August 4, 2014
Amendment	August 13, 2014
Amendment	September 16, 2014
Amendment (labeling)	October 1, 2014
Amendment (labeling)	October 8, 2014

7. NAME & ADDRESS OF APPLICANT:

Name: Galderma Research and Development, LLC  
Address: 5 Cedar Brook Drive, Suite 1  
Cranbury, NJ 08512  
Representative: Elaine Clark, Senior Director, US Regulatory Submissions  
1450 I North Freeway  
Fort Worth, TX 76177  
Telephone: 817-961-5492

8. DRUG PRODUCT NAME/CODE/TYPE:

## CMC Review Data Sheet

- a) Proprietary Name: Soolantra  
b) Non-Proprietary Name (USAN): Ivermectin  
c) Code Name/# (ONDQA only): None  
d) Chem. Type/Submission Priority (ONDQA only):  
• Chem. Type: 3  
• Submission Priority: S

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

10. PHARMACOL. CATEGORY: Anti-inflammatory / Antiparasitic

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: 1%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name:

- Component H<sub>2</sub>B<sub>1a</sub>:
- 1) Avermectin A<sub>1a</sub>, 5-*O*-demethyl-22,23-dihydro-;
  - 2) (2*aE*,4*E*,8*E*)-(5'*S*, 6*S*, 6'*R*, 7*S*, 11*R*, 13*R*, 15*S*, 17*aR*, 20*R*, 20*aR*,20*bS*)-6'-(*S*)-*sec*-Butyl-3', 4', 5', 6, 6', 7, 10,11,14,15,17*a*,20,20*a*,20*b*-tetradecahydro-20, 20*b*-dihydroxy[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*pg*][2,6]benzodioxacyclooctadecin-13, 2'-[2*H*]pyran]-7-yl 2,6-dideoxy-4-*O*-(2,6-dideoxy-3-*O*-methyl- $\alpha$ -L-*arabino*-hexopyranosyl)-3-*O*-methyl- $\alpha$ -L-*arabino*-hexopyranoside.

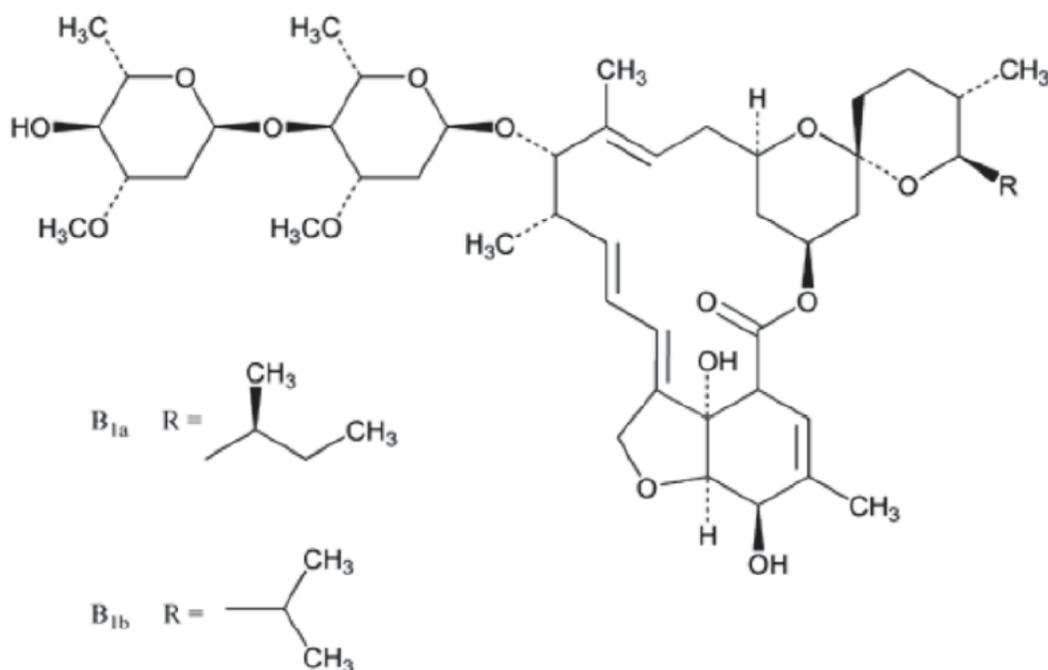
## CMC Review Data Sheet

- Component H<sub>2</sub>B<sub>1b</sub>: 1) Avermectin A<sub>1a</sub>, 5-*O*-demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl)-;  
 2) (2*aE*,4*E*,8*E*)-(5'*S*, 6*S*, 6'*R*, 7*S*, 11*R*, 13*R*, 15*S*, 17*aR*, 20*R*,20*aR*,20*bS*)-3', 4',5',6,6',7,10,11,-oxospiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*pg*] [2,6] benzodioxacyclooctadecin-13,2'[2*H*]pyran]-7-yl 2,6-dideoxy-4-*O*-(2,6-dideoxy-3-*O*-methyl- $\alpha$ -L-arabino-hexopyranosyl)-3-*O*-methyl- $\alpha$ -L-arabino-hexopyranoside.

Molecular formula: Component H<sub>2</sub>B<sub>1a</sub>: C<sub>48</sub>H<sub>74</sub>O<sub>14</sub>  
 Component H<sub>2</sub>B<sub>1b</sub>: C<sub>47</sub>H<sub>72</sub>O<sub>14</sub>

Molecular weight: Component H<sub>2</sub>B<sub>1a</sub>: 875.09  
 Component H<sub>2</sub>B<sub>1b</sub>: 861.07

Structural formula:



CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	March 14, 2014*	Review by J. Wetzel, HFD-627
	II			1	Adequate	August 12, 2014	Review for this submission
	III			1	Adequate	October 25, 2002	Review by J. S. Hathaway
	III			1	Adequate	June 6, 2014	Review for this submission
	III			1	Adequate	June 6, 2014	Review for this submission
	III			1	Adequate	June 11, 2014	Review for this submission

\* - One amendment to this DMF has been submitted since this review. The amendment does not affect the current status of this DMF regarding this application.

<sup>1</sup> 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")

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

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND		
NDA		

## CMC Review Data Sheet

## 18. STATUS:

**ONDQA:**

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics	NA		
EES	Acceptable	8/14/2014	Christina Capacci-Daniel
Pharm/Tox	NA		
Biopharm	Approval	8/28/2014	Kelly Kitchens, Ph.D.
LNC	NA		
Methods Validation	NA, according to the current ONDQA policy		
DMETS	NA		
EA	Categorical exclusion (see review)	12/24/2013	
Microbiology	Approval	3/7/2014	Vinayak B. Pawar, Ph.D.

## Executive Summary Section

# The CMC Review for NDA 206255

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

At this time the applicant has submitted sufficient information to assure the identity, strength, purity, and quality of the drug product.

The Office of Compliance has made an overall “Acceptable” recommendation for the facilities involved in this application.

All labels / labeling are satisfactorily resolved from the CMC perspective.

Therefore, from the ONDQA perspective, this NDA is recommended for approval.

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

Not applicable.

### II. Summary of CMC Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### (1) Drug Substance

Ivermectin is a white to yellowish-white crystalline powder at room temperature. It is also used in two currently marketed drug products: Stromectol<sup>®</sup> Tablets 3 mg (oral) (NDA 50742) as an antiparasitic agent and Sklice<sup>®</sup> Lotion 0.5% (topical) (NDA 202736) as a pediculicide.

Ivermectin is a mixture of two closely related compounds, H<sub>2</sub>B<sub>1a</sub> and H<sub>2</sub>B<sub>1b</sub>. They are present in ivermectin in a proportion of 90% (H<sub>2</sub>B<sub>1a</sub>) to 10% (the drug substance specification indicates that the proportion of H<sub>2</sub>B<sub>1a</sub> is at least 90%). Ivermectin is produced from avermectin, which is a highly active broad-spectrum anti-parasitic agent isolated from the fermentation products of *Streptomyces avermitilis*. Ivermectin is produced specifically from avermectin components B<sub>1a</sub> and B<sub>1b</sub>.

(b) (4)

## Executive Summary Section

Manufacturing process for ivermectin along with most other drug substance information is provided in DMF (b) (4). Both DMF have been reviewed and contain adequate information to support approval of this NDA.

In this drug product, ivermectin is used as an anti-inflammatory agent.

**(2) Drug Product**

The drug product is a cream in which ivermectin drug substance is present in a concentration of 1%. The cream is considered (b) (4) (b) (4) (b) (4)

(b) (4)

The drug product is for treatment of rosacea and it is formulated for patients with sensitive and irritated skin, intended to improve patient comfort and hence compliance.

(b) (4)

The drug product is filled into (b) (4) tubes. The volume of the tubes used for commercial marketing are 30g, 45g, and 60g, with child-resistant (“push and turn” CR) closure. The volume of the tubes used for samples are 2g and 5g with non-CR closures. The tubes are made of (b) (4)

(b) (4)

The expiration dating period for the commercial product (30, 45, and 60g tubes) and for samples in the 5g tube is 36 months, while that for samples in the 2g tube is 18 months.

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

Soolantra<sup>®</sup> (ivermectin 1%) cream is intended to be used as an anti-inflammatory and indicated for once daily topical treatment of inflammatory lesions of rosacea in adults 18 years of age or older.

## Executive Summary Section

According to section 2.6.1 of the NDA (Nonclinical Summary Introduction) the once daily treatment would use up to 1 gram of drug product (10 mg of ivermectin drug substance).

**C. Basis for Approvability or Not-Approval Recommendation**

The information provided in the NDA submission as summarized in the previous section is adequate to support the identity, strength, purity, and quality of the drug product. An "Acceptable" recommendation for the inspection of facilities responsible for the manufacture of the drug substance and drug product was made by the Office of Compliance on August 14, 2014. Labels/Labeling submitted for the drug product are acceptable. Therefore, the NDA may be approved from a CMC perspective.

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

Raymond P. Frankewich -S

Digitally signed by Raymond P. Frankewich -S  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=1300093657, cn=Raymond P.  
Frankewich -S  
Date: 2014.10.14 11:51:08 -04'00'

Raymond P. Frankewich, Ph.D., Branch IV, ONDQA, DNDQAII.

**B. Endorsement Block:**

Moojhong Rhee -A

Digitally signed by Moojhong Rhee -A  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,  
cn=Moojhong Rhee -A, 0.9.2342.19200300.100.1.1=1300041261  
Date: 2014.10.14 13:16:18 -04'00'

Moo Jhong Rhee, Ph.D., Branch Chief, Branch IV, ONDQA, DNDQAII.

**C. CC Block:** entered electronically in Panorama

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# Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre- Marketing Applications (Original)

- I. Review Cover Sheet
- II. Application Detail
- III. Filing Checklist
- IV. Manufacturing Summary
- V. Overall Conclusions and Recommendations

## I. Review Cover Sheet

- 1. OMPQ Reviewer: Christina Capacci-Daniel
- 2. NDA/BLA Number: NDA 206255  
Submission Date: December 20, 2013  
21<sup>st</sup> C. Review Goal Date:  
PDUFA Goal Date: October 20, 2014

### 3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Soolantra
Established or Non-Proprietary Name (USAN) and strength:	Ivermectin
Dosage Form:	Cream, 1%

### 4. SUBMISSION PROPERTIES:

Review Priority :	STANDARD
Applicant Name:	Galderma Research and Development Inc.
Responsible Organization (OND Division):	DDDP

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

## II. Application Detail

1. INDICATION: Topical treatment of inflammatory lesion of rosacea in adults.
2. ROUTE OF ADMINISTRATION: Topical
3. STRENGTH/POTENCY: Cream, 1%
4. Rx/OTC DISPENSED:   Rx       OTC
5. ELECTRONIC SUBMISSION (yes/no)?
6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V	<input checked="" type="checkbox"/>			
2.	Breakthrough Therapy Designation		<input checked="" type="checkbox"/>		
3.	Orphan Drug Designation		<input checked="" type="checkbox"/>		
4.	Unapproved New Drug		<input checked="" type="checkbox"/>		
5.	Medically Necessary Determination		<input checked="" type="checkbox"/>		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		<input checked="" type="checkbox"/>		
7.	Rolling Submission		<input checked="" type="checkbox"/>		
8.	Drug/device combination product with consult		<input checked="" type="checkbox"/>		
9.	Complex manufacturing		<input checked="" type="checkbox"/>		
10.	Other (e.g., expedited for an unlisted reason)		<input checked="" type="checkbox"/>		

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

### III. FILING CHECKLIST

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

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	Yes	No	Comment
11.	Is all site information complete (e.g., contact information, responsibilities, address)?	<input checked="" type="checkbox"/>		
12.	Do all sites indicate they are ready to be inspected (on 356h)?	<input checked="" type="checkbox"/>		(b) (4) was added to the 356h
13.	Is a single comprehensive list of all involved facilities available in one location in the application?	<input checked="" type="checkbox"/>		All sites are listed in an updated attachment to the 356h
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	<input checked="" type="checkbox"/>		DS and DP testing done at the manufacturing sites.
15.	Additional notes (non-filing issue)	<input checked="" type="checkbox"/>		
	1. Are all sites registered or have FEI #?			
	2. Do comments in EES indicate a request to participate on inspection(s)?		<input checked="" type="checkbox"/>	
	3. Is this first application by the applicant?		<input checked="" type="checkbox"/>	

\*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQuestions. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

<b>B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
16.	Have any Comparability Protocols been requested?		<input checked="" type="checkbox"/>	

<b>IMA CONCLUSION</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
17.	Does this application fit one of the EES Product Specific Categories?		<input checked="" type="checkbox"/>	
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?	<input checked="" type="checkbox"/>		
19.	<b>From a CGMP/facilities perspective, is the application fileable?</b>  If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	<input checked="" type="checkbox"/>		

## IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			
Nanotechnology <input type="checkbox"/>	RTRT Proposal <input type="checkbox"/>	PAT <input type="checkbox"/>	Drug/Device Combo <input type="checkbox"/>
PET <input type="checkbox"/>	Design Space <input type="checkbox"/>	Continuous Mfg <input type="checkbox"/>	Naturally derived API <input type="checkbox"/>
Other (explain):	None		

### Manufacturing Highlights

#### 1. Drug Substance

Parameter	Yes	No	Comment
Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		<input checked="" type="checkbox"/>	<ul style="list-style-type: none"> <li>• DMF (b) (4)</li> <li>• Avermectin is produced by fermentation</li> <li>• The DS Ivermectin is synthesized from Avermectin (b) (4)</li> <li>• (b) (4)</li> </ul>

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

(b) (4)



OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

**2. Drug Product**

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		<input checked="" type="checkbox"/>	<ul style="list-style-type: none"><li>• [Redacted] (b) (4)</li><li>• [Redacted]</li><li>• [Redacted]</li><li>• [Redacted]</li></ul>

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

(b) (4)

**3. Facility-Related Risks (e.g., expected in-process testing not being performed, questionable development, unexplained stability failures, data integrity issues, etc.). Describe any potential 21CFR 211 compliance issues.**

- There are no facility issues at this time.

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

**4. Drug Product Facility Inspectional History that could impact the manufacturing of this product**

- There are no drug product facility issues at this time.

**Additional information not covered above**

(b) (4)

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

**Manufacturing Facilities Chart**

Establishment Name	FEI Num	District Short	Country Code	Responsibilities	Profile Code	Inspection History, Dates, Classifications	Most Recent Milestone	Most Recent EER Compliance Status	Comment
(b) (4)				DS intermediate by fermentation	CFN	VAI (b) (4) CFN & CSN	OC RECOMMENDATION	AC	(b) (4) inspection for this DS
				DS manufacture and testing	CFN	NAI (b) (4) CFN & CSN	OC RECOMMENDATION	AC	Recent surveillance inspection
				DS manufacture and testing	CSN	NAI (b) (4) CSN	OC RECOMMENDATION	AC	Recent surveillance inspection
GALDERMA PRODUCTION CANADA, INC.	3003671557	AME	CAN	DP manufacture and testing	(b) (4)	NAI 5/17/2013, (b) (4)	OC RECOMMENDATION	AC	Recent surveillance inspection

## V. Overall Conclusions and Recommendations

<b>Is the application fileable?</b> (yes/no, Yes to questions 11-12) YES
<b>Based on Section IV, is a KTM warranted for any PAI? (yes/no). If yes, please identify the sites in the above chart.</b> <ul style="list-style-type: none"><li>• PAI's waived.</li></ul>
<b>Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities?</b> (yes/no)
Comments for 74 Day Letter
1.
2.
3.

## REVIEW AND APPROVAL (DARRTS)

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

CHRISTINA A CAPACCI-DANIEL  
02/20/2014

VIPULCHANDRA N DHOLAKIA  
02/20/2014

ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications

## IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **NDA 206255**

2. DATES AND GOALS:

Letter Date: <b>Dec. 20, 2013</b>	Submission Received Date : <b>Dec. 20, 2013</b>
PDUFA Goal Date: <b>Oct. 20, 2014</b>	

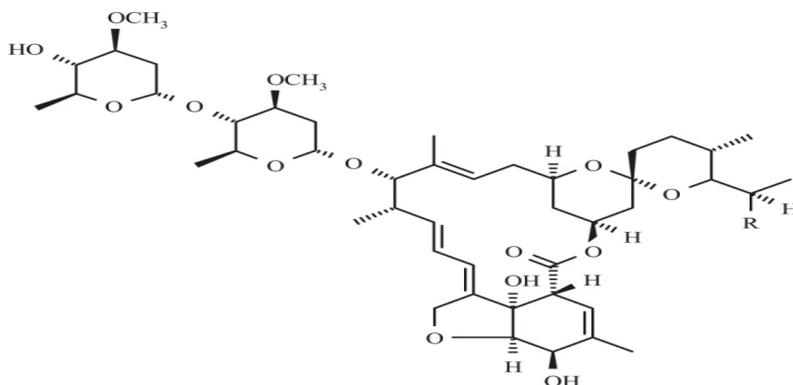
3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Soolantra
Established or Non-Proprietary Name (USAN):	Ivermectin
Dosage Form:	Cream
Route of Administration	Topical
Strength/Potency	1%
Rx/OTC Dispensed:	Rx

4. INDICATION:

Treatment of inflammatory lesions of rosacea

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



Component H2B1a: R = CH<sub>2</sub>CH<sub>3</sub>  
Empirical formula: C<sub>48</sub>H<sub>74</sub>O<sub>14</sub>  
Molecularweight: 875

Component H2B1b: R = CH<sub>3</sub>  
C<sub>47</sub>H<sub>72</sub>O<sub>14</sub>  
861

It contains not less than 95.0 percent and not more than 102.0 percent for the sum of component H2B1a plus component H2B1b, (b) (4) and the ratio (calculated by area percentage) of component H2B1a/(H2B1a + H2B1b) is not less than 90.0 percent.

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

6. NAME OF APPLICANT (as indicated on Form 356h):

Galderma Research and Development

7. SUBMISSION PROPERTIES:

Review Priority:	Standard
Submission Classification (Chemical Classification Code):	Type 3
Application Type:	505(b)(2)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	Division of Dermatology and Dental Products
Other Information	

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		x	
Clinical Pharmacology		x	
Establishment Evaluation Request (EER)	x		Submitted on Jan. 23, 2014
Pharmacology/Toxicology		x	
Methods Validation			Numerous related substances with complicated structures. To be determined after in-depth review by CMC reviewer
Environmental Assessment		x	Categorical exclusion claimed.
CDRH		x	
Other	x		Quality Microbiology assignment made on 1/23/14. Vinayak Pawar has been assigned as product quality microbiology reviewer for this submission.

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

## Overall Filing Conclusions and Recommendations

### CMC:

<b>Is the Product Quality Section of the application fileable from a CMC perspective?</b> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>
CMC Filing Issues: 1. None

<b>Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter?</b> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>
CMC Comments for 74-Day Letter: 1. Provide a representative sample (2 units) for each to-be-marketed packaging configuration, and each non-child-resistant configuration studied in the supporting stability studies. 2. Provide 6 months of stability data (long term and accelerated) for the registration stability batches including microscopic appearance data. Provide photos from the microscopic appearance test. 3. Provide microscopic appearance data for all supporting registration stability batches, including the photos. 4. Clarify which manufacturing process (Phase 3 or commercial process) was used in the manufacture of European clinical supplies.

### Biopharmaceutics:

<b>Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective?</b> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>
Biopharmaceutics Filing Issues: 1. None

<b>Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter?</b> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>
Biopharmaceutics Comments for 74-Day Letter: <ul style="list-style-type: none"><li>• Provide the in vitro release testing (IVRT) method development and validation reports. The IVRT method development report should contain (but is not limited to) justification for the selection of the following methodology components:<ol style="list-style-type: none"><li>a. Diffusion apparatus</li><li>b. Receptor medium selection</li><li>c. Membrane selection</li><li>d. Sampling time points</li><li>e. Temperature</li></ol></li><li>• The IVRT method validation report should contain (but is not limited to) the</li></ul>

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

following validation components:

- a. Linearity and Range
  - b. Accuracy/Precision and Reproducibility
  - c. Mass Balance & Dose Depletion
  - d. Sensitivity and Specificity
  - e. Selectivity
  - f. Robustness
  - g. Membrane Inertness
  - h. Receptor Solution Solubility/Stability
- The IVRT method's sensitivity, specificity, selectivity and robustness need to be performed with altered product lots that contain 50% and 150% of the label claim of active pharmaceutical ingredient (API) in the reference product, with the test evaluating a minimum of one run of 6 diffusion cells each per product concentration, including the reference.
  - Submit all the generated data in electronic format (e.g. MS Excel) as described below:

Chamber ID: # (identify each cell assignment)

Sample volume removed: mL

Diffusion cell area: cm<sup>2</sup>

Time (min, hr, etc.)	Sq. rt. Time	Concentration in Cell (µg/mL)	Amount in Cell (µg)	Cumulative Amount in Cell (µg)	Cumulative Diffusion (µg/cm <sup>2</sup> )
T1					
T2					
T3					
T4					
T5					
Tn					

## Microbiology:

**Is the Product Quality Section of the application fileable from a Microbiology perspective?**

Yes  No

Microbiology Filing Issues:

See Microbiology Filing Review for details and for any potential Microbiology review issues. The assigned Quality Micro reviewer is Vinayak Pawar.

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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**Summary of Initial Quality Assessment**

<b>Does the submission contain any of the following elements?</b>			
Nanotechnology	QbD Elements	PET	Other, please explain
No	No	No	No

<b>Is a team review recommended?</b>	Yes	No <input checked="" type="checkbox"/>
Suggested expertise for team: n/a		

**Summary of Critical Issues and Complexities**

1. Equivalence of registration stability batches to Phase 3 and supporting stability batches

There are two major differences between registration stability batches and Phase 3 and supporting stability batches: Registration stability batches were made using commercial manufacturing process and packaged in the to-be-marketed container/closure system (child-resistant) whereas Phase 3 and supporting stability batches were made using Phase 3 manufacturing process and packaged in non-child-resistant container/closure system.

Note that the process change made post Phase 3 resulted in batches with (b) (4) (b) (4) (b) (4) An IVRT study was conducted to support the process change. **A critical review will need to be performed on the IVRT study.**

Also note that registration stability batches were not used in any clinical studies. Furthermore, only three months of stability data from the registration stability batches were provided in the NDA. The specification setting and shelf-life projection would mainly rely on the data from the supporting stability batches. **The applicability of stability data from supporting batches to the registration stability batches will need a critical review.** It is also important to point out that a grain of salt will need to be taken when utilizing accelerated stability data to project shelf-life at room temperature for this semi-solid product. This is because in addition to chemical stability there is also physical stability to be considered. Very little information has been provided regarding the physical structure of this cream. (b) (4)

2.

(b) (4)

3. Drug Product related substances method validation

This needs a critical review because there are numerous related substances with complicated structures. Pending an in-depth review by the primary CMC reviewer, the method may need to be sent to OTR lab for evaluation.

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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4. Droplet size test

Droplet size (NMT (b)(4)) is included in the proposed specification for the (b)(4) as a part of the test of Microscopic Appearance. The test may need to be added to the drug product regulatory specification.

5. Establishment Information

DMF (b)(4) is referenced by the applicant for CMC information of the drug substance ivermectin. DMF (b)(4) references to VMF (b)(4) for the source of avermectin. (b)(4). Both DMF (b)(4) and VMF (b)(4) were reviewed in Oct/Nov 2011 and found to be adequate to support the approval of Sklice lotion (NDA 202736).

No LOA is provided in this NDA to authorize FDA for an access to VMF (b)(4). The Agency contacted the holder of DMF (b)(4), on Feb. 7, 2014 through a teleconference. In the teleconference, (b)(4) agreed to provide an LOA issued by the holder of VMF (b)(4) (b)(4) in the week of Feb. 10, 2014 for this NDA. A statement of readiness for inspection will be provided with the LOA. (b)(4) also agreed to notify the NDA applicant, Galderma, of all facilities involved in the manufacture of ivermectin including (b)(4) (b)(4).

An IR letter to Galderma is also being processed to request the submission of all relevant establishment information involved in the manufacture of avermectin, and a statement of readiness for inspection for each establishment applicable to this NDA, including those relevant to the manufacture of avermectin.

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

**Initial Quality Assessment**

The proposed drug substance, ivermectin USP, is a semi-synthetic, antiparasitic agent derived from the avermectins, a class of highly active broad-spectrum, anti-parasitic agents isolated from the fermentation products of *Streptomyces avermitilis*. (b) (4)

DMF (b) (4)

The DMF was most recently deemed adequate to support the approval of Sklice lotion (NDA 202736) in November, 2011. DMF (b) (4) references VMF (b) (4) for the source of ivermectin. VMF (b) (4) was reviewed on Oct. 24, 2011 and found to be adequate to support the approval of Sklice lotion (NDA 202736). The applicant (Topaz Pharmaceuticals) of Sklice lotion NDA provided an LOA to reference the VMF for CMC information.

The proposed drug product, Soolantra (ivermectin) cream, 1% (w/w) is a white to pale yellow homogeneous cream packaged in white laminated tubes with a (b) (4) head and white (b) (4) closure. The proposed trade sizes are 30 g, 45 g and 60 g, and sample sizes are 2g and 5 g. The trade sizes are packaged with a child-resistant closure but the sample sizes are with non-child-resistant closure. Multiple suppliers are proposed for the container/closure systems. The table below shows the supplier(s) for each packaging configuration:

Size	Sample size		Trade size		
	2 g	5 g	30 g	45 g	60 g
Feature	Non-child-resistant closure	Non-child-resistant closure	Child-resistant "push and turn" closure	Child-resistant "push and turn" closure	Child-resistant "push and turn" closure
Container/Closure System Supplier	(b) (4)				

The to-be-marketed formulation (table on the next page) is the same formulation used in Phase 3 clinical trials and registration stability batches. All excipients are compendial. The formulation contains no novel excipients and no excipients are derived from animal origin.

The proposed commercial manufacturing scale is (b) (4). The proposed commercial drug product manufacturing site, GPI in Canada, is also the manufacturing site of Phase 3 supplies and registration stability batches. The commercial drug product manufacturing process consists of the following steps:

(b) (4)

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

(b) (4)

**Formulation Composition for the Proposed To-Be-Marketed Formulation**

Formulation No. 575.754	% (w/w)	mg/g	Function <sup>a</sup>	Pharmacopeia Reference
<b>Active Ingredient</b>				
Ivermectin	1.0	10	Drug substance	USP
<b>Excipients</b>				
Glycerin	(b) (4)	(b) (4)	(b) (4)	USP
Isopropyl palmitate	(b) (4)	(b) (4)	(b) (4)	USP-NF
Carbomer copolymer (type B)	(b) (4)	(b) (4)	(b) (4)	USP-NF
Dimethicone (b) (4)	(b) (4)	(b) (4)	(b) (4)	USP-NF
Edetate disodium	(b) (4)	(b) (4)	(b) (4)	USP
Citric acid monohydrate	(b) (4)	(b) (4)	(b) (4)	USP-NF
Cetyl alcohol	(b) (4)	(b) (4)	(b) (4)	USP-NF
Stearyl alcohol	(b) (4)	(b) (4)	(b) (4)	USP-NF
Polyoxyl 20 cetostearyl ether	(b) (4)	(b) (4)	(b) (4)	USP-NF
Sorbitan monostearate	(b) (4)	(b) (4)	(b) (4)	USP-NF
Methylparaben	(b) (4)	(b) (4)	(b) (4)	USP-NF
Propylparaben	(b) (4)	(b) (4)	(b) (4)	USP-NF
Phenoxyethanol	(b) (4)	(b) (4)	(b) (4)	USP-NF
Propylene glycol	(b) (4)	(b) (4)	(b) (4)	USP
Oleyl alcohol	(b) (4)	(b) (4)	(b) (4)	USP-NF
Sodium hydroxide (b) (4)	(b) (4)	(b) (4)	(b) (4)	USP-NF
Purified water	(b) (4)	(b) (4)	(b) (4)	USP

Stability data provided in the initial submission to support the proposed expiration dating period are three months of long term (25°C//60%RH), intermediate (30°C//75%RH), and accelerated temperature (40°C//75%RH) data from three registration stability batches. The registration stability batches are commercial scale, made at the designated commercial site using the commercial process and packaged in the to-be-marketed container/closure systems. The proposed storage condition is 20°-25°C with excursions permitted to 15°-30°C (USP controlled room temperature). The proposed expiration dating period is 36 months for the fill sizes of 5g, 30 g, 45 g and 60 g, and 18 months for the 2 g sample size.

Additional supporting stability data (long term, intermediate, and accelerated) up to 36 months from multiple commercial scale batches are also provided to support the proposed expiration dating period. These supporting stability data, although quite substantial, are from batches packaged in non-child-resistant container/closure systems (i.e. not to-be-marketed). Furthermore, these supporting batches were made using a phase 3 process which is slightly different from the commercial process. The applicant claims that container/closure systems and manufacturing process used in the manufacture of these supporting stability batches are equivalent to those of the registration stability batches.

Results of in-use stability, photostability, and freeze/thaw studies are also provided to support storage/handling of the product. These studies were conducted using registration stability batches.

**Biopharmaceutics Filing Review**

The NDA is fileable from Biopharmaceutics perspective. See Biopharm filing review authored by Kelly Kitchens for NDA 206255.

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

**FILING REVIEW CHECKLIST**

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:

<b>A. GENERAL</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
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>B. FACILITIES*</b>				
<b>* 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.</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
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? <b>This question is not applicable for synthesized API.</b>		x	Although the facility responsible for the manufacture of avermectin is not provided in the initial submission. (b) (4) has agreed in a teleconference to notify the NDA applicant of the existence of the facility. An IR is also being processed to request NDA applicant to provide all relevant establishment information (including the statement of readiness for inspection) involved in the manufacture of avermectin, which is manufactured by fermentation.

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
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"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	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"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?		x	<p>The statement for (b) (4) is still outstanding. However, (b) (4) has verbally agreed to provide it in the week of Feb. 10, 2014. An IR is also being processed to request NDA applicant to provide all relevant establishment information (including the statement of readiness for inspection) involved in the manufacture of avermectin, which is manufactured by fermentation.</p>

<b>C. ENVIRONMENTAL ASSESMENT</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	Has an environmental assessment or claim of categorical exclusion been provided?	x		Categorical exclusion claimed based on EIC below 1 ppb.

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

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
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		
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?			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		
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?			n/a
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?			n/a

<b>F. METHODS VALIDATION (MV)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
29.	Is there a methods validation package?		x	Procedures and their validations reports are provided in the Regional section.

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

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

<b>H. MASTER FILES (DMF/MAF)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
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)	9/2/13	
	II		10/8/13		
	III		6/5/12, 10/3/13, 10/8/13	Each letter is for a (b) (4)	
	III		6/19/13, 11/12/13	Each letter is for a (b) (4)	

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

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

*{See appended electronic signature page}*

Shulin Ding  
CMC-Lead  
Division II  
Office of New Drug Quality Assessment

*{See appended electronic signature page}*

Kelly Kitchens  
Biopharmaceutics Reviewer  
Office of New Drug Quality Assessment

*{See appended electronic signature page}*

Tapash Ghosh  
Biopharmaceutics Team Leader  
Office of New Drug Quality Assessment

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Moo-Jhong Rhee  
Branch Chief  
Division II  
Office of New Drug Quality Assessment

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

/s/  
-----

SHULIN DING  
02/07/2014

MOO JHONG RHEE  
02/10/2014  
Chief, Branch IV

\* Completed 10/21/14 in Panorama  
so no signature page.



**CMC REVIEW**



**NDA 206255**

**Soolantra<sup>®</sup> (ivermectin) Cream, 1%**

**Galderma Research and Development, LLC**

**Raymond P. Frankewich, Ph.D.**

**Review Chemist**

**Office of New Drug Quality Assessment  
Division of New Drug Quality Assessment II  
Branch IV**

**CMC REVIEW  
For the Division of Dermatology and Dental Products  
(CDER/ODEIII/DDDP, HFD-540)**



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CMC Review Data Sheet

# CMC Review Data Sheet

- 1. NDA 206255
- 2. REVIEW #: 1
- 3. REVIEW DATE: 9-October-2014
- 4. REVIEWER: Raymond P. Frankewich, Ph.D.
- 5. PREVIOUS DOCUMENTS: None
- 6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	December 24, 2013
Correspondence (C)	
Amendment	February 17, 2014
Amendment	March 31, 2014
Amendment	April 18, 2014
Amendment	April 23, 2014
Amendment	June 27, 2014
Amendment	July 18, 2014
Amendment	August 4, 2014
Amendment	August 13, 2014
Amendment	September 16, 2014
Amendment (labeling)	October 1, 2014
Amendment (labeling)	October 8, 2014

7. NAME & ADDRESS OF APPLICANT:

Name: Galderma Research and Development, LLC  
 Address: 5 Cedar Brook Drive, Suite 1  
 Cranbury, NJ 08512  
 Representative: Elaine Clark, Senior Director, US Regulatory Submissions  
 1450 I North Freeway  
 Fort Worth, TX 76177  
 Telephone: 817-961-5492

8. DRUG PRODUCT NAME/CODE/TYPE:



## CMC Review Data Sheet

- a) Proprietary Name: Soolantra  
b) Non-Proprietary Name (USAN): Ivermectin  
c) Code Name/# (ONDQA only): None  
d) Chem. Type/Submission Priority (ONDQA only):  
    • Chem. Type: 3  
    • Submission Priority: S

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

10. PHARMACOL. CATEGORY: Anti-inflammatory / Antiparasitic

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: 1%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED:  Rx  OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Not a SPOTS product

## 1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name:

- Component H<sub>2</sub>B<sub>1a</sub>: 1) Avermectin A<sub>1a</sub>, 5-*O*-demethyl-22,23-dihydro-;  
2) (2*aE*,4*E*,8*E*)-(5'*S*, 6*S*, 6'*R*, 7*S*, 11*R*, 13*R*, 15*S*, 17*aR*, 20*R*, 20*aR*,20*bS*)-6'-(*S*)-*sec*-Butyl-3', 4', 5', 6, 6', 7, 10,11,14,15,17*a*,20,20*a*,20*b*-tetradecahydro-20, 20*b*-dihydroxy[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*pg*][2,6]benzodioxacyclooctadecin-13, 2'-[2*H*]pyran]-7-yl 2,6-dideoxy-4-*O*-(2,6-dideoxy-3-*O*-methyl- $\alpha$ -L-*arabino*-hexopyranosyl)-3-*O*-methyl- $\alpha$ -L-*arabino*-hexopyranoside.

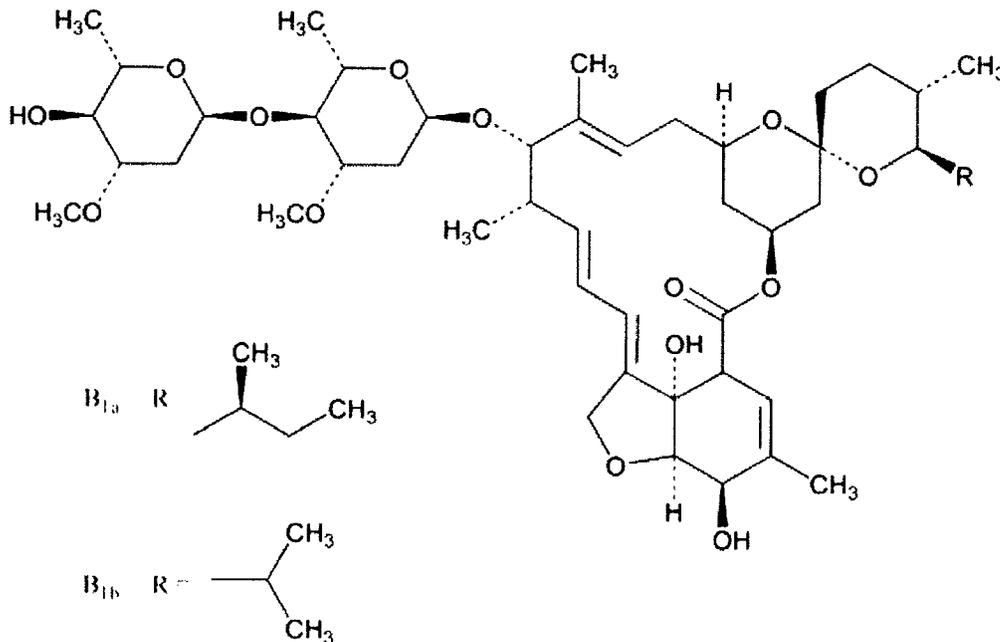
CMC Review Data Sheet

- Component H<sub>2</sub>B<sub>1b</sub>: 1) Avermectin A<sub>1a</sub>, 5-*O*-demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl)-;  
 2) (2*aE*,4*E*,8*E*)-(5'*S*, 6*S*, 6'*R*, 7*S*, 11*R*, 13*R*, 15*S*, 17*aR*, 20*R*,20*aR*,20*bS*)-3', 4',5',6,6',7,10,11,-oxospiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*pg*] [2,6] benzodioxacyclooctadecin-13,2'[2*H*]pyran]-7-yl 2,6-dideoxy-4-*O*-(2,6-dideoxy-3-*O*-methyl- $\alpha$ -L-arabino-hexopyranosyl)-3-*O*-methyl- $\alpha$ -L-arabino-hexopyranoside.

Molecular formula: Component H<sub>2</sub>B<sub>1a</sub>: C<sub>48</sub>H<sub>74</sub>O<sub>14</sub>  
 Component H<sub>2</sub>B<sub>1b</sub>: C<sub>47</sub>H<sub>72</sub>O<sub>14</sub>

Molecular weight: Component H<sub>2</sub>B<sub>1a</sub>: 875.09  
 Component H<sub>2</sub>B<sub>1b</sub>: 861.07

Structural formula:



CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	March 14, 2014*	Review by J. Wetzel, HFD-627
	II			1	Adequate	August 12, 2014	Review for this submission
	III			1	Adequate	October 25, 2002	Review by J. S. Hathaway
	III			1	Adequate	June 6, 2014	Review for this submission
	III			1	Adequate	June 6, 2014	Review for this submission
	III			1	Adequate	June 11, 2014	Review for this submission
	III			1	Adequate	June 11, 2014	Review for this submission

\* - One amendment to this DMF has been submitted since this review. The amendment does not affect the current status of this DMF regarding this application.

<sup>1</sup> 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")

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

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND		
NDA		



## CMC Review Data Sheet

## 18. STATUS:

**ONDQA:**

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics	NA		
EES	Acceptable	8/14/2014	Christina Capacci-Daniel
Pharm/Tox	NA		
Biopharm	Approval	8/28/2014	Kelly Kitchens, Ph.D.
LNC	NA		
Methods Validation	NA, according to the current ONDQA policy		
DMETS	NA		
EA	Categorical exclusion (see review)	12/24/2013	
Microbiology	Approval	3/7/2014	Vinayak B. Pawar, Ph.D.

# The CMC Review for NDA 206255

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

At this time the applicant has submitted sufficient information to assure the identity, strength, purity, and quality of the drug product.

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

All labels / labeling are satisfactorily resolved from the CMC perspective.

Therefore, from the ONDQA perspective, this NDA is recommended for approval.

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

Not applicable.

### II. Summary of CMC Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### (1) Drug Substance

Ivermectin is a white to yellowish-white crystalline powder at room temperature. It is also used in two currently marketed drug products: Stromectol<sup>®</sup> Tablets 3 mg (oral) (NDA 50742) as an antiparasitic agent and Sklice<sup>®</sup> Lotion 0.5% (topical) (NDA 202736) as a pediculicide.

Ivermectin is a mixture of two closely related compounds, H<sub>2</sub>B<sub>1a</sub> and H<sub>2</sub>B<sub>1b</sub>. They are present in ivermectin in a proportion of 90% (H<sub>2</sub>B<sub>1a</sub>) to 10% (the drug substance specification indicates that the proportion of H<sub>2</sub>B<sub>1a</sub> is at least 90%). Ivermectin is produced from avermectin, which is a highly active broad-spectrum anti-parasitic agent isolated from the fermentation products of *Streptomyces avermitilis*. Ivermectin is produced specifically from avermectin components B<sub>1a</sub> and B<sub>1b</sub>.

(b) (4)

## Executive Summary Section

Manufacturing process for ivermectin along with most other drug substance information is provided in DMF (b) (4). Both DMF have been reviewed and contain adequate information to support approval of this NDA.

In this drug product, ivermectin is used as an anti-inflammatory agent.

**(2) Drug Product**

The drug product is a cream in which ivermectin drug substance is present in a concentration of 1%. The cream is considered (b) (4) emulsion. (b) (4)

The drug product is for treatment of rosacea and it is formulated for patients with sensitive and irritated skin, intended to improve patient comfort and hence compliance.

The drug product is filled into (b) (4) tubes. The volume of the tubes used for commercial marketing are 30g, 45g, and 60g, with child-resistant ("push and turn" CR) closure. The volume of the tubes used for samples are 2g and 5g with non-CR closures. The tubes are made of (b) (4)

The expiration dating period for the commercial product (30, 45, and 60g tubes) and for samples in the 5g tube is 36 months, while that for samples in the 2g tube is 18 months.

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

Soolantra<sup>®</sup> (ivermectin 1%) cream is intended to be used as an anti-inflammatory and indicated for once daily topical treatment of inflammatory lesions of rosacea in adults 18 years of age or older.



## Executive Summary Section

According to section 2.6.1 of the NDA (Nonclinical Summary Introduction) the once daily treatment would use up to 1 gram of drug product (10 mg of ivermectin drug substance).

**C. Basis for Approvability or Not-Approval Recommendation**

The information provided in the NDA submission as summarized in the previous section is adequate to support the identity, strength, purity, and quality of the drug product. An "Acceptable" recommendation for the inspection of facilities responsible for the manufacture of the drug substance and drug product was made by the Office of Compliance on August 14, 2014. Labels/Labeling submitted for the drug product are acceptable. Therefore, the NDA may be approved from a CMC perspective.

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

Raymond P. Frankewich -S

Digitally signed by Raymond P. Frankewich -S  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=1300093657, cn=Raymond P.  
Frankewich -S  
Date: 2014.10.14 11:51:08 -04'00'

Raymond P. Frankewich, Ph.D., Branch IV, ONDQA, DNDQAII.

**B. Endorsement Block:**

Moojhong Rhee -A

Digitally signed by Moojhong Rhee -A  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,  
cn=Moojhong Rhee -A, 0.9.2342.19200300.100.1.1=1300041261  
Date: 2014.10.14 13:16:18 -04'00'

Moo Jhong Rhee, Ph.D., Branch Chief, Branch IV, ONDQA, DNDQAII.

**C. CC Block:** entered electronically in Panorama

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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VINAYAK B PAWAR  
01/31/2014

JOHN W METCALFE  
01/31/2014  
I concur.