

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207589Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

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

Date: October 13, 2015

From: Yichun Sun, Ph.D.

**Application Technical Lead, Branch V
Division of New Drug Products II
Office of New Drug Products**

Through: Moo-Jhong Rhee, Ph.D.

**Chief, Branch V
Division of New Drug Products II
Office of New Drug Products**

To: CMC Review #1 of NDA 207589

Subject: Final Approval Recommendation for NDA 207589

At the time when the CMC review #1 was written, resolution of issues on **Labels and Labeling** was pending. Additionally, the facility review team from the Office of Process and Facilities had not issued an overall "Acceptable" recommendation for the facilities involved in this application.

Label/Labeling

On October 9, 2015, the NDA applicant submitted an amendment providing the finalized mock up container and carton labels. Additionally, the applicant also agreed to all the CMC changes made to the package insert. All the labels/labeling issues are now **satisfactorily resolved**. The CMC sections of the final package insert, and mock up container and carton labels are attached (**Attachment - 1**).

Establishment Evaluation

On September 3, 2015, the facility review team provided an **Overall Acceptable** recommendation for the facilities involved in the manufacture and test of the drug substance and drug product. The review is attached (**Attachment - 2**).

Recommendation:

All pending issues on CMC and Label/Labeling are now satisfactorily resolved for the NDA, and the facility review team from the Office of Process and Facilities provided an **Overall Acceptable** recommendation for the facilities involved in the manufacture and test of the drug substance and drug product. Therefore, from the ONDP's perspective, this NDA is recommended for **APPROVAL**. An expiration dating period of **24 months** is granted for the drug product of NDA 207589.

Application Technical Lead's Assessment and Signature

The NDA is recommended for approval from quality perspective.

Yichun Sun, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
10/13/2015

Yichun
Sun -S

Digitally signed by Yichun Sun -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yichun Sun -S, 0.9.2342.19200300.100.1.1=1300393310
Date: 2015.10.13 12:20:39 -04'00'

Attachment - 1 (CMC Sections of the Finalized Labeling and Labels)

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

Date: October 9, 2015
From: Sarah Ibrahim, Ph.D.
Reviewer, Branch V/DNDP II
ONDP
Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Product II
ONDP
To: CMC Review #1 of NDA 207589
Subject: Final Labeling Review

The CMC review #1 has noted labeling issues unresolved.

On October 9, 2015, the final label and labeling were submitted and the deficiencies previously noted are resolved satisfactorily from the ONDP perspective. (See the attached final labels/labeling.)

Review Notes

Previous Deficiencies

I. "Highlights" Section

- Proprietary and established name, dosage form and dosage administration should be modified to include (b) (4)

ENSTILAR® (calcipotriene and betamethasone dipropionate) Foam,
0.005%/0.064%

- "Dosage forms and strengths" should be as follows:

Foam contains 52.2 mcg calcipotriene hydrate (equivalent to 50 mcg of calcipotriene) and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone)

Resolution: Dosage forms and strength was modified as follows:

DOSAGE FORMS AND STRENGTHS _____
Foam, 0.005%/0.064%

Each gram of Enstilar® Foam contains 52.2 mcg calcipotriene hydrate (equivalent to 50 mcg of calcipotriene) and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone). (3)

2. #16 How supplied/storage and Handling

- Include 1 X 60 gram for NDC 50222-302-60

Resolution:

The following was included:

Enstilar® Foam is available in aluminum cans of:

- 1 x 60 g (NDC 50222-302-60)
- 2 x 60 g (NDC 50222-302-66)

3. # 17 should include the manufacturer/distributor as per 21 CFR 201.1

Resolution:

The following was included:

Manufactured by:

Colep Laupheim GmbH & Co. KG

Fockestraße 12

88471 Laupheim

Germany (DE)

Distributed by:

LEO Pharma Inc.

1 Sylvan Way,

Parsippany, NJ 07054

4. Immediate Container Label:

- The expiration date is not displayed on the label, however it is to be included on the bottom of the can.

Resolution:

The expiration date on the bottom of the can is deemed acceptable.

- The Strength expressed should contain statement indicating that the expressed strength is after propellant evaporation (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))

Resolution:

The following statement is included:

After the propellants (dimethyl ether and butane) have evaporated, each gram of Enstilar® Foam contains 52.2 mcg calcipotriene hydrate (equivalent to 50 mcg of calcipotriene) and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone)

5. Carton Labeling

- Bar Code per 21 CFR 201.25(c)(2) is not displayed for NDC 50222-302-60 carton.

Resolution:

Bar code displayed for NDC 50222-302-60 Carton.

- “See package insert for dosage information” is not included on carton and in violation of (21 CFR 201.55).

Resolution:

21 CFR 201.55 states that “compliance with this requirement would be met by a statement such as "See package insert for dosage information" (highlight added). As currently presented “Usual Dosage: See Prescribing Information” meets this criteria. This is found acceptable.

Attachment: Copies of final labeling/labels



(b) (4)

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

Reviewer's Assessment and Signature:

The final label and labeling were submitted and the deficiencies previously noted are resolved satisfactorily from the ONDP perspective.

Reviewer's Signature
Sarah Ibrahim, Ph.D.
Branch V
Division of New Drug Products II/ONDP

Sarah
Ibrahim -S

Digitally signed by Sarah Ibrahim -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Sarah Ibrahim -S,
0.9.2342.19200300.100.1.1=200159
1303
Date: 2015.10.09 16:03:42 -04'00'

10/9/2015

Secondary Review Comments and Concurrence:

I concur with Dr. Sarah Ibrahim's assessment on the labels and labeling.

Supervisor's Signature
Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Products II/ONDP
10/9/2015


10/9/15

Attachment - 2 (Facility review)



ASSESSMENT OF THE FACILITIES

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

S.2.1 Manufacturer(s)

1. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment name	FEI Number	Responsibilities and profile codes	Current status	Initial Risks Identified	Final Recommendation
LEO Pharma A/S	3002807496	CSN: Calcipotriol monohydrate API manufacturer and tester	No PAI recommended	High risk (due to an irrelevant OAI)	Acceptable based on inspectional history and experience
	(b) (4)	CSN: Betamethasone dipropionate API manufacturer and tester	No PAI recommended	Low risk	Acceptable based on inspectional history and experience
		CSN: Betamethasone dipropionate API (b) (4)	No PAI recommended	Low risk	Acceptable based on inspectional history

Reviewer's Assessment:

Leo Pharma A/S, Ballerup, Denmark | FEI 3002807496

The firm proposes to manufacture the calcipotriol monohydrate API component of the fixed combination drug product LEO 90100 aerosol foam according to the process described in the DMF 10514. The API (b) (4) are identical to (b) (4) (b) (4) the currently approved ointment (under NDA 21852) (b) (4) (b) (4). The DMF 10514 was determined adequate to support three additional NDAs, all of which were approved to market fixed combination drug products containing calcipotriol monohydrate and betamethasone dipropionate.

Pre-approval coverage of the API to support NDA 21852 occurred in August 2005, after

which time the application was approved (2006) and commercial production of the API commenced. The firm continues to manufacture the API with consistent inspectional outcomes which provide reasonable assurance that the facility is in an adequate state of control. The reader should note that a 2009 inspection resulted in an OAI classification (upgraded from an initial VAI) and issuance of an Untitled Letter to reflect significant deficiencies observed for the manufacture of a sterile product which was subsequently discontinued in the U.S. market in 2011. A review of the 483 issued in 2009 shows that one observation was made about (b) (4) which contains the (b) (4) (b) (4) there were no deficiencies observed for the manufacture of the actual API.

The OAI did result in an artificial “high risk” initial profile, but this is because the classification was applied across all profiles and all PACs. A review of the inspectional history for the (b) (4) manufacture shows the firm continues to remain in a state of control. Previous citations about the API manufacturing were confirmed as corrected during subsequent inspections.

While the initial risk profile suggests a PAI is needed (due to the OAI), a review of the firm’s inspectional history and experience with the identical API precludes the need for such. **This facility is considered acceptable to manufacture the calcipotriol (b) (4) API to support NDA 207589.**

(b) (4)

**2.3.P DRUG PRODUCT****2.3.P.3 Manufacture*****P.3.1 Manufacturer(s)***

2. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment name	FEI Number	Responsibilities and profile codes	Current status	Initial Risks Identified	Final Recommendation
		(b) (4)	PAI conducted July 2015	No FDA history High risk	Acceptable based on pre-approval inspection
LEO Laboratories, Ltd.	3002807468	OIN: Manufacturer, tester of bulk (b) (4)	No PAI recommended	Low	Acceptable based on inspectional history and experience

(b) (4)

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page



QUALITY ASSESSMENT



Based on the pre-approval inspection findings and the firm's response to the 483, the facility is considered acceptable to manufacture the LEO 90100 aerosol foam drug product to support NDA 207589.

Leo Laboratories, Dublin, Ireland | FEI 3002807468

The firm proposes to manufacture the bulk (b) (4)

The process (b) (4) described in NDA 21852 which is currently approved for the manufacture of Taclonex ointment. A review of the firm's inspection history indicates consistent coverage of the Taclonex product and reveals a process that is under an adequate state of control. The firm's inspectional history and experience with the (b) (4) preclude the need for a pre-approval inspection as reflected by the "low" risk from the initial risk assessment. **This facility is considered acceptable to manufacture the bulk (b) (4) to support NDA 207589.**

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

There appear to be no significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facility's inspection results, inspectional history, and relevant experience. The facilities are determined acceptable to support approval of NDA 207589.

Juandria Williams, PhD
Acting QAL, OPF/DIA/B3
September 3, 2015

Juandria Williams -S
Digitally signed by Juandria Williams -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000459158, cn=Juandria Williams -S
Date: 2015.09.03 12:51:06 -04'00'

Secondary Review Comments and Concurrence:

Concur
Grace E. McNally, Acting Branch Chief, OPF/DIA/B3
September 3, 2015

Grace E. McNally -S
Digitally signed by Grace E. McNally -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300042045, cn=Grace E. McNally -S
Date: 2015.09.03 12:52:35 -04'00'



QUALITY ASSESSMENT



Recommendation:

This 505(b)(2) NDA is *not* deemed ready for approval as of this review in its present form per 21 CFR 314.125(b)(6),(13).

NDA 207589 Review #1

Drug Name/Dosage Form	Calcipotriene and betamethasone dipropionate foam
Strength	0.005%/0.064%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	LEO Pharma A/S
US agent, if applicable	LEO Pharma Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original submission	December 18, 2014

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Debasis Ghosh	Branch II/Division of New Drug API
Drug Product	Sarah Ibrahim	Branch V/Division of New Drug Products II
Process	Erin Kim	Branch VIII/Division of Process Assessment III
Microbiology	Erika Pfeiler	Branch I/Division of Microbiology Assessment
Facility	Juandria Williams	Branch III/Division of Inspection Assessment
Biopharmaceutics	Haritha Mandula	Branch II/Division of Biopharmaceutics
Project/Business Process Manager	Melinda Bauerlien	Branch I/Division of Regulatory and Business Process Management
Application Technical Lead	Yichun Sun	Branch V/Division of New Drug Products II
Laboratory (OTR)	NA	NA
ORA Lead	Paul Perdue	Division of Medical Products & Tobacco Operations
Environmental Assessment (EA)	NA	NA

Table of Contents

Table of Contents	2
Quality Review Data Sheet.....	3
Executive Summary.....	5
Primary Quality Review.....	9
ASSESSMENT OF THE DRUG SUBSTANCE	9
2.3.S DRUG SUBSTANCE	9
ASSESSMENT OF THE DRUG PRODUCT.....	18
2.3.P DRUG PRODUCT	18
R.2 Comparability Protocols.....	46
ASSESSMENT OF THE PROCESS.....	49
2.3.P DRUG PRODUCT	49
R.2 Comparability Protocols.....	64
ASSESSMENT OF THE FACILITIES	65
2.3.S DRUG SUBSTANCE	65
2.3.P DRUG PRODUCT	66
ASSESSMENT OF THE BIOPHARMACEUTICS	67
ASSESSMENT OF MICROBIOLOGY	83
A APPENDICES	84
A.2 Adventitious Agents Safety Evaluation	84
I. Review of Common Technical Document-Quality (Ctd-Q) Module 1.....	87
II. List of Deficiencies To Be Communicated.....	101
III. Attachments.....	103
IV. Administrative.....	105

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION:

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS ¹	DATE REVIEW COMPLETED	COMMENTS
10514	Type II	LEO Pharma A/S	Calcipotriene hydrate	Adequate	06/29/2015	Last review completed by Debasis Ghosh; no new submission since this review.
(b) (4)	Type II	(b) (4)	(b) (4)	Adequate	07/22/2015	Last review completed by Debasis Ghosh; no new submission since this review.
	Type III (if applicable)			Adequate	8/11/2015	Annual report 7/14/2015
	Type III			Adequate	8/11/2015	There is enough data in the application, therefore the DMF did not need to be reviewed.
	Type III			Adequate	12/30/2014	Last review completed by Theophin Claude; no new submission since this review.
	Type III			Adequate	11/05/2014	Last review completed by Theophin Claude; no new submission since this review.

¹ Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)



QUALITY ASSESSMENT
NDA # 207589



B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	114063	Original IND, Active (as of the date of this review)
Meeting minutes of EOP 2 CMC	114063	Discussion of CMC related questions
Pre-NDA meeting minutes	114063	Discussion of the content and format of the proposed NDA submission for Leo 90100

3. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	----	N/A	----	----
Pharmacology/Toxicology	----	N/A	----	----
CDRH	----	N/A	----	----
Clinical	----	N/A	----	----
Other	----	N/A	----	----

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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

However, the facility reviewers have not made a final “Acceptable” recommendation on the facilities involved.

Also, the issues on labels/labeling are not completely resolved at this time.

Therefore, from the OPQ perspective, this NDA is not ready for approval in its present form per 21 CFR 314.125(b)(6),(13) until the above issues are satisfactorily resolved. (See the **List of Deficiencies** on p. 101-102)

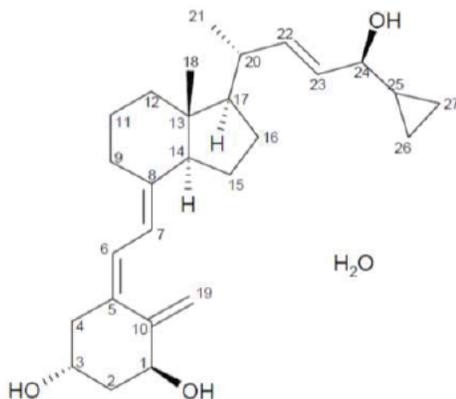
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

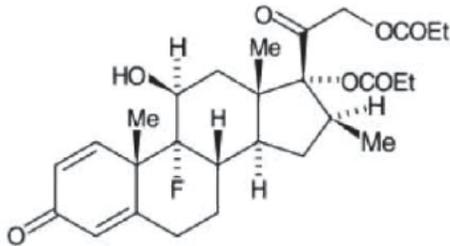
II. Summary of Quality Assessments

A. Drug Substance [calcipotriene and betamethasone dipropionate] Quality Summary

There are two active pharmaceutical ingredients used in the drug product (Calcipotriene and Betamethasone Dipropionate ^{(b) (4)}), namely Calcipotriene and Betamethasone Dipropionate. Calcipotriene hydrate is a synthetic vitamin D3 analog. The chemical name of Calcipotriene hydrate is: 9,10-Secochole-5,7,10(19),22-tetraene-1,3,24-triol-2,4-cyclopropyl-, monohydrate, (1 α , 3 β , 5Z, 7E,22E, 24S). The chemical structure of Calcipotriene monohydrate is:



Betamethasone dipropionate is a synthetic corticosteroid. The chemical name of Betamethasone Dipropionate is: 9-fluoro-11 β ,17,21-trihydroxy-16 β -methylpregna-1,4-diene-3,20-dione 17,21-dipropionate. Its chemical structure is:



Both of the drug substances are chemically synthesized. CMC information of the drug substances is referred to DMFs. CMC information for **calcipotriol** (b)(4) is referred to DMF #10514. CMC information for **Betamethasone Dipropionate** is referred DMF (b)(4). Both of the DMFs have been reviewed and found adequate in supporting their use in the NDA. The recommended retest period for Calcipotriene is (b)(4) months when stored ambient condition in the proposed container closure system. (b)(4). The recommended retest period for Betamethasone Dipropionate is (b)(4) months when stored at ambient condition in the proposed container closure system. (b)(4)

B. Drug Product [Enstilar (calcipotriene and betamethasone dipropionate) Foam] Quality Summary

The drug product, Enstilar[®] (Calcipotriene and Betamethasone Dipropionate) Foam, is a vitamin D analogue and corticosteroid combination product. It is indicated for topical treatment of plaque psoriasis in adults 18 years of age and older. The drug product is a white to off-white opalescent liquid in a pressurized aluminum spray can with a continuous valve and actuator. At administration the product is a white to off-white foam after evaporation of the propellants (dimethyl ether and butane). Each gram of foam contains 52.2 mcg calcipotriene hydrate (equivalent to 50 mcg of calcipotriene) and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone) in a base of white petrolatum, polypropylene glycol stearyl ether, mineral oil, all-rac-alpha-tocopherol, and butylhydroxytoluene. (b)(4)

(b)(4)



The identity, strength, purity including microbial limits, and quality of the drug product are deemed assured by the drug product specification. The development of in vitro release test (IVRT) of Calcipotriol and Betamethasone Dipropionate from Taclonex® ointment has been carried out. However, it was not possible, despite extensive efforts, to develop and validate an IVRT method to demonstrate the sameness between Taclonex® ointment batches due to high variability of the in vitro release rates of Calcipotriol and Betamethasone Dipropionate. Therefore, the applicant's position that an IVRT specification is not feasible to be implemented as a quality control tool at release and during stability studies is acceptable. The expiration dating period of 24 months is recommended for the drug product when stored at 20 - 25°C based on the 12-month long-term and 6-month accelerated stability data obtained from 3 registration batches of the drug product.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	ENSTILAR®
Non Proprietary Name of the Drug Product	N/A
Non Proprietary Name of the Drug Substance	Calcipotriene and Betamethasone Dipropionate
Proposed Indication(s) including Intended Patient Population	Enstilar® Foam is a vitamin D analogue and corticosteroid combination product indicated for the topical treatment of plaque psoriasis in adults 18 years of age and older.
Duration of Treatment	Once daily for up to 4 weeks.
Maximum Daily Dose	The maximum weekly dose should not exceed (b) (4) g
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

1. BCS Classification:
 - Drug Substance: N/A
 - Drug Product: N/A

2. Biowaivers/Biostudies:
 - Biowaiver Requests: N/A
 - PK studies: N/A
 - IVIVC: N/A
 - IVRT:

The NDA applicant tried to develop an in vitro release test (IVRT) for Calcipotriol and Betamethasone Dipropionate from Taclonex® ointment. However, it was not possible, despite extensive efforts, to develop and validate an IVRT method to demonstrate the sameness between Taclonex® ointment batches due to high variability of the in vitro release rates of Calcipotriol and Betamethasone Dipropionate. Therefore, the applicant's position that an IVRT specification is not feasible to be implemented as a quality control tool at release and during stability studies is acceptable. However, the applicant should consider how they might bridge post-approval changes in the absence of an IVRT method.

E. Novel Approaches

N/A

F. Any Special Product Quality Labeling Recommendations

Shake Enstilal® can prior to using.

G. Process/Facility Quality Summary (see Attachment A)

H. Life Cycle Knowledge Information (see Attachment B)

Yichun
Sun -S

Digitally signed by Yichun Sun
-S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Yichun Sun -S,
0.9.2342.19200300.100.1.1=13
00393310
Date: 2015.09.01 12:06:31
-04'00'

56 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page



**QUALITY ASSESSMENT
NDA # 207589**



Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment: The NDA does not contain any comparability protocols.

OVERALL ASSESSMENT AND SIGNATURES: PROCESS

Reviewer's Assessment and Signature:

Acceptable. No further Process questions at this time.

Reviewer's Signature

Erin Kim, Ph.D.
Branch VIII
Division of Process Assessment III/OPF
8/10/2015

**Erin M.
Kim -S**

Digitally signed by Erin M. Kim -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Erin M. Kim -S,
0.9.2342.19200300.100.1.1=1300
396749
Date: 2015.08.24 18:06:39 -04'00'

Supervisor Comments and Concurrence:

I concur.

Supervisor's Signature

Nallaperumal Chidambaram, Ph.D.
Chief, Branch VIII
Division of Process Assessment III/OPF
08/10/2015

**Nallaperuma
I
Chidambara
m -S**

Digitally signed by
Nallaperumal Chidambaram -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=13
00133922, cn=Nallaperumal
Chidambaram -S
Date: 2015.08.25 10:07:08
-04'00'

ASSESSMENT OF THE FACILITIES

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

Manufacturer(s)

14. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment	FEI Number	Responsibilities and	Current status	Initial Risks	Final
---------------	------------	----------------------	----------------	---------------	-------



**QUALITY ASSESSMENT
NDA # 207589**



name		profile codes		Identified	Recommendation
Leo Pharma A/S	3002807496	CSN: Calcipotriol monohydrate API manufacturer and tester	No PAI recommended	None	Acceptable based on inspectional history and experience
	(b) (4)	CSN: Betamethasone dipropionate API manufacturer and tester	No PAI recommended	None	Acceptable based on inspectional history and experience
		CSN: Betamethasone dipropionate API (b) (4)	No PAI recommended	None	Acceptable based on inspectional history

Reviewer's Assessment:

2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

Manufacturer(s)

15. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment name	FEI Number	Responsibilities and profile codes	Current status	Initial Risks Identified	Final Recommendation
	(b) (4)	OIN: Manufacturer, tester of finished drug product	PAI conducted July 2015	No FDA history	Pending PAI evaluation
Leo Laboratories, Ltd.	3002807468	OIN: Manufacturer, tester of drug product intermediate	No PAI recommended	None	Acceptable based on inspectional history and experience

Reviewer's Assessment:

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES



**QUALITY ASSESSMENT
NDA # 207589**



Reviewer's Assessment and Signature:

Supervisor Comments and Concurrence:

ASSESSMENT OF THE BIOPHARMACEUTICS

16. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

In the 74-day letter (dated March 2, 2015), the applicant was asked to develop an in vitro release test (IVRT) methodology and propose in vitro release acceptance criteria (range) for their drug product to be used systemically at release and during stability testing as a quality control parameter.

Applicant's Response:



(b) (4)

14 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page



**QUALITY ASSESSMENT
NDA # 207589**



Applicant's Response:



(b) (4)

Reviewer's Assessment:

There are no changes to the formulation, manufacturing process or manufacturing site changes from the development phase to the commercial setting; therefore, no bridging studies are needed.

**OVERALL ASSESSMENT AND SIGNATURES:
BIOPHARMACEUTICS**

Reviewer's Assessment and Signature:

The application is recommended for approval for a Biopharmaceutics standpoint.

Reviewer's Signature:

**Haritha Mandula, Ph.D.
Branch II
Division of Biopharmaceutics/ONDP
7/28/2015**

Kelly Lee
8/31/2015

Secondary Review Comments and Concurrence:

I have reviewed the Biopharmaceutics Assessment and concur with the Reviewer's conclusions.

Secondary Reviewer's Signature

Kelly Kitchens, Ph.D.
QAL, Branch II
Division of Biopharmaceutics/ONDP
7/28/2015

Kelly M.
Kitchens -S

Digitally signed by Kelly M. Kitchens - S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000336574, cn=Kelly M. Kitchens - S
Date: 2015.08.18 13:52:00 -04'00'

ASSESSMENT OF MICROBIOLOGY

18. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Calcipotriene and Betamethasone Dipropionate is a foam for topical administration. The product is intended for multiple uses, and its formulation (b) (4). This product (b) (4) (b) (4) the previously approved NDA 021852 (Taclonex Ointment), with the ointment (referred to in the application as the "(b) (4)") dissolved in dimethyl ether and butane to make a foam product.

The applicant proposes a waiver of microbial limits testing for drug product release and stability, based on product formulation and control of microbiological quality for excipients used to manufacture the ointment intermediate. Further, the applicant states that in a (b) (4) year period of Taclonex Ointment manufacturing (which comprises the ointment intermediate used in the manufacture of the subject product) no microbial counts have been observed over the limit of detection of (b) (4).

The drug product was tested for microbial limits during development using methods described in USP Chapter <61> and USP Chapter <62>. Specifications for this testing were consistent with those described in USP <1111>, which for this type of product include a total aerobic microbial count of NMT (b) (4) and a total combined yeast and mold count of (b) (4) as well as the absence of *Staphylococcus aureus* and *Pseudomonas ae* per gram. The microbial limits test methods were verified to be appropriate for use with the drug product following procedures consistent with those in USP Chapter <61> and <62>.

The applicant did not perform antimicrobial effectiveness testing on this multi-use drug product; rather, asserted that due to the product's (b) (4), this testing is not necessary. Further, the applicant asserts that the product categories described in USP (b) (4), providing further support for the assertion that antimicrobial effectiveness testing is not necessary for these products.

Reviewer's Assessment:

ADEQUATE

REVIEWER COMMENT – Microbial survival and proliferation in the drug product is very unlikely (b) (4)

(b) (4) he applicant provided a suitable rationale for a waiver of microbial limits testing and for antimicrobial effectiveness testing. Information about control/testing for *Burkholderia cepacia* was not requested from this applicant (b) (4) product formulation.

The applicant proposes a waiver of microbial limits testing for drug product release and stability, and provides a suitable rationale to support this proposal.

19. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment: N/A

A APPENDICES

A.2 Adventitious Agents Safety Evaluation



QUALITY ASSESSMENT
NDA # 207589



20. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment: N/A

21. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment: N/A

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: Adequate

Reviewer's Signature

Erika Pfeiler, Ph.D.

Branch I

Division of Microbiology Assessment/OPF

8/10/2015

Erika Pfeiler
8/30/2015



**QUALITY ASSESSMENT
NDA # 207589**



Supervisor Comments and Concurrence: I concur with the microbiology assessment and conclusions.

Supervisor's Signature

Stephen E. Langille, Ph.D.

Chief, Branch I

Division of Microbiology Assessment/OPF

8/10/2015

**Stephen
E. Langille
-S**

Digitally signed by Stephen E. Langille -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300151320, cn=Stephen E. Langille -S
Date: 2015.08.18 12:39:28 -04'00'

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

(b) (4)



Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	ENSTILAR® (calcipotriene and betamethasone dipropionate) (b) (4) Foam, 0.005%/0.064%	Proprietary name has not yet been approved. The established name is presented correctly. (b) (4) is not the correct description. Not Satisfactory.
Dosage form, route of administration	Enstilar® (b) (4) Foam for topical use	The dosage form "Foam" is described adequately. (b) (4) is not the correct description. Not Satisfactory.
Controlled drug	NA	NA

substance symbol (if applicable)		
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	<p>(b) (4), Foam, 0.005%/0.064% Each gram of Enstilar® (b) (4) Foam contains 52.2 mcg calcipotriene hydrate (equivalent to 50 mcg of calcipotriene) and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone).</p>	<p>The "Foam" dosage form is clearly described. (b) (4) is not the correct description. The strength is adequately described. Not Satisfactory.</p>

Conclusion:

1. Proprietary name has not yet been approved.
2. The dosage form is clearly described and adequately summarized.
3. The term (b) (4) is to be removed.

This section is **Not Satisfactory**.

(b) “Full Prescribing Information” Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer’s Assessment
Available dosage forms	(b)(4), Foam, 0.005%/0.064%	Dosage form described correctly. (b)(4) is not the correct description. Not Satisfactory
Strengths: in metric system	After the propellants have evaporated, each gram of Enstilar® (b)(4) Foam contains 52.2 mcg calcipotriene hydrate (equivalent to 50 mcg of calcipotriene) and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone).	The strength is described correctly. (b)(4) is not the correct description. Not Satisfactory.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Enstilar® (b)(4) Foam is a white to off-white opalescent liquid in a pressurized aluminum spray can with a continuous valve and actuator. At administration the product is a white to off-white (b)(4) foam.	The foam is described correctly. (b)(4) is not the correct description. Not Satisfactory

Conclusion:

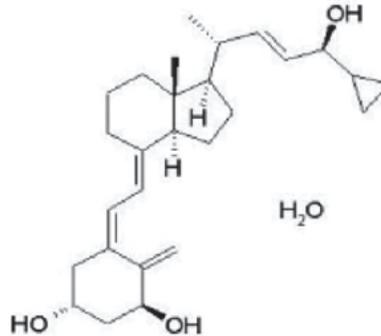
1. The description of the identifying characteristics of the (b)(4) foam dosage form, including container description, color and consistency of foam after propellant evaporation is adequately expressed.
2. (b)(4) is not the correct description.

This section is **Not Satisfactory**.

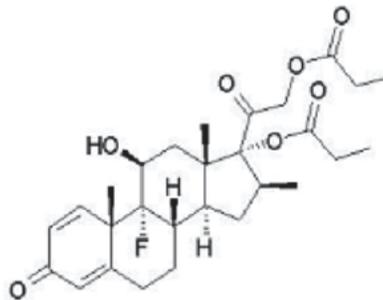
#11: Description (21CFR 201.57(c)(12))

11 DESCRIPTION

Enstilar® (b) (4) Foam contains calcipotriene hydrate and betamethasone dipropionate. It is intended for topical use only. Calcipotriene hydrate is a synthetic vitamin D3 analog. Chemically, calcipotriene hydrate is 9,10-secochola-5,7,10(19),22-tetraene-1,3,24-triol,24-cyclo-propyl-monohydrate, (1 α ,3 β ,5Z,7E,22E,24S) with the empirical formula C₂₇H₄₀O₃·H₂O, a molecular weight of 430.6, and the following structural formula:



Calcipotriene hydrate is a white to almost white, crystalline compound. Betamethasone dipropionate is a synthetic corticosteroid. Betamethasone dipropionate has the chemical name pregna-1,4-diene-3,20-dione-9-fluoro-11-hydroxy-16-methyl-17,21-bis(1-oxypropoxy)-(11 β ,16 β), with the empirical formula C₂₈H₃₇FO₇, a molecular weight of 504.6, and the following structural formula:



Betamethasone dipropionate is a white to almost white crystalline powder. (b) (4)

After the propellants (dimethyl ether and butane) (b) (4), each gram of Enstilar® (b) (4) Foam contains 52.2 mcg calcipotriene hydrate (equivalent to 50 mcg of calcipotriene) and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone) in a base of white petrolatum, PPG-11 stearyl ether, mineral oil, all rac- alpha-tocopherol, and butylhydroxytoluene. Enstilar® (b) (4) Foam is a white to off-white opalescent liquid in a pressurized aluminum spray can with a continuous valve and actuator. At administration the product is a white to off-white (b) (4) foam.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	ENSTILAR® (calcipotriene and betamethasone dipropionate) (b) (4) Foam, 0.005%/0.064%	Proprietary name has not yet been approved. The established name is presented correctly. Not Satisfactory.
Dosage form and route of administration	(b) (4) foam for topical use only.	The dosage form "foam" and route are expressed correctly. (b) (4) is not the correct description. Not Satisfactory.
Active moiety expression of strength with equivalence statement for salt (if applicable)	After the propellants (dimethyl ether and butane) have evaporated, each gram of Enstilar® (b) (4) Foam contains 52.2 mcg calcipotriene hydrate (equivalent to 50 mcg of calcipotriene) and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone)	The strength is expressed correctly. (b) (4) is not the correct description. Not Satisfactory.
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Propellants: Dimethyl ether and butane, and a base of white petrolatum, PPG-11 stearyl ether, mineral oil, all-rac-alpha-tocopherol, and butylhydroxytoluene.	The inactive ingredients information is presented correctly. Satisfactory.
Statement of being sterile (if applicable)	NA	NA
Pharmacological/ therapeutic class	Calcipotriene hydrate is a synthetic vitamin D3 analog. Betamethasone dipropionate is a synthetic corticosteroid.	This will be determined in the labeling meeting.
Chemical name, structural formula, molecular weight	Calcipotriene hydrate is 9,10-secochola-5,7,10(19),22-tetraene-1,3,24-triol,24-cyclo-propyl-mono hydrate, (1 α ,3 β ,5Z,7E,22E,24S) with the empirical formula C ₂₇ H ₄₀ O ₃ ·H ₂ O, a molecular weight of 430.6. Betamethasone dipropionate has the chemical name pregna-1,4-diene-3,20-dione-9-fluoro-11-hydroxy-16-methyl-17,21-bis(1-oxypropoxy)-(11 β ,16 β), with the empirical formula C ₂₈ H ₃₇ FO ₇ , a molecular weight of 504.6.	The chemical names and the structural formula are correct. Satisfactory.
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa, solubility, or pH)	NA	NA

Conclusion:

1. The chemical structures and formula are expressed correctly.
2. The strength of the dosage form is expressed correctly with proper description including propellant evaporation and strength of (b)(4) foam.
3. (b)(4) is not the correct description.

This section is **Not Satisfactory**.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))**16.1 How Supplied**

Enstilar[®] (b)(4) Foam is a white to off-white opalescent liquid in a pressurized aluminum spray can with a continuous valve and actuator. At administration the product is a white to off-white (b)(4) foam.

Enstilar[®] Aerosol Foam is available in aluminum cans of:

- 60 g (NDC 50222-302-60)
- 2 x 60 g (NDC 50222-302-66)

16.2 Storage

- Store Enstilar[®] (b)(4) Foam at 20°- 25°C (68° -77°F); excursions permitted between 15°-30°C (59°-86°F).
- Contents under pressure. Do not puncture or incinerate. Do not expose to heat or store at temperatures above 120°F (49°C). Do not freeze.
- The product should be used within six months after it has been opened.

16.3 Handling

- (b)(4) foam is flammable; avoid heat, flame or smoking when using this product.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Not included	This information is not provided. Not satisfactory.
Available units (e.g., bottles of 100 tablets)	Enstilar® (b)(4) Foam is a white to off-white opalescent liquid in a pressurized aluminum spray can with a continuous valve and actuator. At administration the product is a white to off-white (b)(4) foam.	This information is provided. (b)(4) is not the correct description. Not Satisfactory
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Enstilar® (b)(4) Foam is available in aluminum cans of: <ul style="list-style-type: none"> 60 g (NDC 50222-302-60) 2 x 60 g (NDC 50222-302-66) 	This information is provided. (b)(4) is not the correct description. Not Satisfactory
Special handling (e.g., protect from light, do not freeze)	<ul style="list-style-type: none"> Shake before use. (b)(4) foam is flammable; avoid heat, flame or smoking when using this product. Keep out of the reach of children. 	This information is provided. (b)(4) is not the correct description. Not Satisfactory
Storage conditions	<ul style="list-style-type: none"> Store Enstilar® (b)(4) Foam at 20- 25°C (68- 77°F); excursions permitted between 15°-30°C (59°- 86°F). Contents under pressure. Do not puncture or incinerate. Do not expose to heat or store at temperatures above 120°F (49°C). Do not freeze. The product should be used within six months after it has been opened. 	This information is provided. (b)(4) is not the correct description. Not Satisfactory

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Information not listed in Section 17 of package insert	Not Satisfactory.

Conclusion:

1. The strength of the dosage form is not included under section 16.
2. The package insert section 17 does not include the manufacturer/distributor name.
3. (b)(4) is not the correct description.

This section is **Not Satisfactory.**

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



QUALITY ASSESSMENT
NDA # 207589



Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Enstilar® (calcipotriene and betamethasone dipropionate) (b) (4) Foam, 0.005%/0.064%	Proprietary name has not yet been approved. The established name is presented correctly. (b) (4) is not the correct description. Not Satisfactory.
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	(calcipotriene and betamethasone dipropionate) (b) (4) Foam, 0.005%/0.064%	(b) (4) is not the correct description. Not Satisfactory.
Route of administration (21.CFR 201.100(b)(3))	For Topical Use Only	Satisfactory.
Net contents* (21 CFR 201.51(a))	Net Wt. 60 g	Satisfactory.
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	After the propellants (dimethyl ether and butane) have evaporated, each gram of Enstilar® (b) (4) Foam contains 52.2 mcg calcipotriene hydrate (equivalent to 50 mcg of calcipotriene) and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone) in a base of white petrolatum, PPG-11 stearyl ether, mineral oil, all-rac-alpha-tocopherol, and butylhydroxytoluene.	(b) (4) is not the correct description. Satisfactory.
Lot number per 21 CFR 201.18	Displayed	Satisfactory
Expiration date per 21 CFR 201.17	Not displayed on the label. To be included on bottom of the can.	Not satisfactory.
"Rx only" statement per 21 CFR 201.100(b)(1)	The statement is prominently displayed.	Satisfactory
Storage (not required)	The statement is prominently displayed.	Satisfactory
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC 50222-302-60 NDC 50222-302-66 (b) (4)	Satisfactory Satisfactory Not included in insert.
Bar Code per 21 CFR 201.25(c)(2)***	Barcode not displayed on label.	Refer to Carton Label
Name of manufacturer/distributor (21 CFR 201.1)	Displayed	Satisfactory

Others

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled “sample”, “physician’s sample”, or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of “oral” from the container label

**Not required for Physician’s samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion:

- 1- The expiration date is not displayed on the label, however it is to be included on the bottom of the can.
- 2- The Strength expressed should contain statement indicating that the expressed strength is after propellant evaporation (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))
- 3- (b)(4) is not the correct description.

This Section is **Not Satisfactory**.

2) Carton Labeling

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



QUALITY ASSESSMENT
NDA # 207589



Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Enstilar® (calcipotriene and betamethasone dipropionate) (b) (4) Foam, 0.005%/0.064% (calcipotriene and betamethasone dipropionate)	The proprietary name has not yet been approved. (b) (4) is not the correct description. Not Satisfactory
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	(b) (4) Foam, 0.005%/0.064%	(b) (4) is not the correct description. Not Satisfactory
Net contents (21 CFR 201.51(a))	Displayed	Satisfactory
Lot number per 21 CFR 201.18	Displayed	Satisfactory
Expiration date per 21 CFR 201.17	Displayed	Satisfactory
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	After the propellants (dimethyl ether and butane) have evaporated, each gram of Enstilar® (b) (4) Foam contains 52.2 mcg calcipotriene hydrate (equivalent to 50 mcg of calcipotriene) and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone) in a base of white petrolatum, PPG-11 stearyl ether, mineral oil, all-rac-alpha-tocopherol, and butylhydroxytoluene.	(b) (4) is not the correct description. Not Satisfactory
Sterility Information (if applicable)	NA	NA
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Displayed	Satisfactory
Storage Conditions	Displayed	Satisfactory
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Displayed	Satisfactory
Bar Code per 21 CFR 201.25(c)(2)**	NDC 50222-302-60 (Not displayed) NDC 50222-302-66 (Displayed)	Not satisfactory Satisfactory
Name of manufacturer/distributor	Displayed	Satisfactory
"See package insert for dosage information" (21 CFR 201.55)	Not displayed.	Not Satisfactory
"Keep out of reach of children" (optional for Rx, required for OTC)	Not Displayed	Not required since it is an RX drug. Satisfactory
Route of Administration (not	Displayed.	Satisfactory

required for oral, 21 CFR 201.100(d)(1) and (d)(2))		
--	--	--

Conclusion:

- 1- Bar Code per 21 CFR 201.25(c)(2) is not displayed for NDC 50222-302-60 carton.
- 2- “See package insert for dosage information” is not included on carton and in violation of (21 CFR 201.55).
- 3- (b)(4) is not the correct description.

This section is **Not Satisfactory**.

II. List of Deficiencies To Be Communicated

- A. Drug Substance: None.
- B. Drug Product: None.
- C. Process/Facility: Final “Approval” recommendation has not been made.
- D. Biopharmaceutics: None.
- E. Microbiology: None.
- F. Label/Labeling

The following are deficiencies that need to be resolved:

1. “Highlights” Section
 - Proprietary and established name, dosage form and dosage administration should be modified to include (b)(4) ENSTILAR® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064%
 - “Dosage forms and strengths” should be as follows:
Foam contains 52.2 mcg calcipotriene hydrate (equivalent to 50 mcg of calcipotriene) and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone)
2. #16 How supplied/storage and Handling
 - Include 1 X 60 gram for NDC 50222-302-60
3. # 17 should include the manufacturer/distributor as per 21 CFR 201.1
4. Immediate Container Label:
 - The expiration date is not displayed on the label, however it is to be included on the bottom of the can.

- The Strength expressed should contain statement indicating that the expressed strength is after propellant evaporation (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))
- 5. Carton Labeling
 - Bar Code per 21 CFR 201.25(c)(2) is not displayed for NDC 50222-302-60 carton.
 - “See package insert for dosage information” is not included on carton and in violation of (21 CFR 201.55).

III. Attachments

A. Facility

OVERALL RECOMMENDATION:				
DRUG SUBSTANCE				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION
DRUG PRODUCT				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION

B. Lifecycle Knowledge Management

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/Comments
Assay (calcipotriol and betamethasone dipropionate)	<ul style="list-style-type: none"> Formulation Raw materials Process parameters Scale/equipment Site 	M	A specification limit of not less than (b) (4) % of calcipotriol is therefore set for the (b) (4) to ensure that LEO 90100 will fulfill the proposed specification throughout shelf life.	Acceptable	Both the drug substances are analyzed using an HPLC/UPLC method.
Impurities, calcipotriol	<ul style="list-style-type: none"> Formulation Raw materials Process parameters Scale/equipment Site 	M	The (b) (4) is controlled through requirements to (b) (4) relevant excipients and manufacture in a (b) (4) environment.	Acceptable	(b) (4) % (b) (4) % (b) (4) % Any unspecified impurity (b) (4) % Total (b) (4) %
Impurities, betamethasone dipropionate	<ul style="list-style-type: none"> Formulation Raw materials Process parameters Scale/equipment Site 	M	The (b) (4) is controlled	Acceptable	Any unspecified impurity (b) (4) % Total (b) (4) %

			through requirements (b) (4)		
(b) (4)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	L	<p>of relevant excipients and manufacture in a (b) (4) environment.</p> <p>(b) (4) contribution to (b) (4) is high and not moderate and the material attributes of the (b) (4) are unlikely to impact the (b) (4) content.</p>	Acceptable	Low risk to the content of (b) (4)

IVRT:

The NDA applicant tried to develop an in vitro release test (IVRT) for Calcipotriol and Betamethasone Dipropionate from Taclonex® ointment. However, it was not possible, despite extensive efforts, to develop and validate an IVRT method to demonstrate the sameness between Taclonex® ointment batches due to high variability of the in vitro release rates of Calcipotriol and Betamethasone Dipropionate. Therefore, the applicant's position that an IVRT specification is not feasible to be implemented as a quality control tool at release and during stability studies is acceptable. However, the applicant should consider how they might bridge post-approval changes in the absence of a valid IVRT method.

IV. Administrative

A. Reviewer's Signature

B. Endorsement Block

Reviewer Name/Date: [*Same date as draft review*]

Secondary Reviewer Name/Date:

Project Manager Name/Date:

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 207589

Submission Type: NDA

Established/Proper Name:
Enstilar (calcipotriene and
betamethasone dipropionate)

Applicant: LEO Pharma A/S

Letter Date: 12/18/14

Dosage Form: Foam

Chemical Type: Type 3, New
formulation

Stamp Date: 12/18/14

Strength: 0.005%/0.064%

A. FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			N/A
3.	Are there any potential review issues to be forwarded to the Applicant, not including any filing comments stated above?			<ul style="list-style-type: none"> Delivery rate, pressure tests and minimum fill recommended in USP <603>, and microbial limits tests are not included in the drug product specification. Novel excipient, dimethyl ether, is used as a propellant. The HPLC method, which is not stability indicating, used for assay and impurities, was changed during stability studies. Proposed expiration dating period needs to be carefully reviewed because of data variation and analytical method change.

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
Product Type				
1.	New Molecular Entity ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
2.	Botanical ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
3.	Naturally-derived Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
4.	Narrow Therapeutic Index Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.	PET Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
6.	PEPFAR Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7.	Sterile Drug Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
8.	Transdermal ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
9.	Pediatric form/dose ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
10.	Locally acting drug ¹	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
11.	Lyophilized product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
12.	First generic ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
13.	Solid dispersion product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
14.	Oral disintegrating tablet ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
15.	Modified release product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
16.	Liposome product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
17.	Biosimilar product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
18.	Combination Product	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
19.	Other	<input type="checkbox"/>	<input type="checkbox"/>	

Regulatory Considerations					
20.	USAN Name Assigned		<input checked="" type="checkbox"/>	<input type="checkbox"/>	
21.	End of Phase II/Pre-NDA Agreements		<input checked="" type="checkbox"/>	<input type="checkbox"/>	
22.	SPOTS (Special Products On-line Tracking System)		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
24.	Comparability Protocol(s) ²		<input checked="" type="checkbox"/>	<input type="checkbox"/>	
25.	Other		<input type="checkbox"/>	<input type="checkbox"/>	
Quality Considerations					
26.	Drug Substance Overage		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
27.	Design Space	Formulation	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
28.		Process	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
29.		Analytical Methods	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
30.		Other	<input type="checkbox"/>	<input type="checkbox"/>	
31.	Real Time Release Testing (RTRT)		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
32.	Parametric Release in lieu of Sterility Testing		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
33.	Alternative Microbiological Test Methods		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
34.	Process Analytical Technology ¹		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
36.		Excipients	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
37.		Microbial	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
38.	Unique analytical methodology ¹		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
39.	Excipients of Human or Animal Origin		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
40.	Novel Excipients		<input checked="" type="checkbox"/>	<input type="checkbox"/>	
41.	Nanomaterials ¹		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
42.	Hold Times Exceeding 30 Days		<input checked="" type="checkbox"/>	<input type="checkbox"/>	
43.	Genotoxic Impurities or Structural Alerts		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
44.	Continuous Manufacturing		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
45.	Other unique manufacturing process ¹		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		<input checked="" type="checkbox"/>	<input type="checkbox"/>	
47.	New delivery system or dosage form ¹		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
48.	Novel BE study designs		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
49.	New product design ¹		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
50.	Other		<input type="checkbox"/>	<input type="checkbox"/>	

¹Contact Office of Testing and Research for review team considerations

²Contact Post Marketing Assessment staff for review team considerations

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? <input type="checkbox"/> Drug Substance <input type="checkbox"/> Drug Product <input type="checkbox"/> Appendices <ul style="list-style-type: none"> <input type="checkbox"/> Facilities and Equipment <input type="checkbox"/> Adventitious Agents Safety Evaluation <input type="checkbox"/> Novel Excipients <input type="checkbox"/> Regional Information <ul style="list-style-type: none"> <input type="checkbox"/> Executed Batch Records <input type="checkbox"/> Method Validation Package <input type="checkbox"/> Comparability Protocols 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Method Validation Package is not included.
FACILITY INFORMATION					
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? 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? For each site, does the application list: <input type="checkbox"/> Name of facility, <input type="checkbox"/> Full address of facility including street, city, state, country <input type="checkbox"/> FEI number for facility (if previously registered with FDA) <input type="checkbox"/> Full name and title, telephone, fax number and email for on-site contact person. <input type="checkbox"/> Is the manufacturing responsibility and function identified for each facility, and <input type="checkbox"/> DMF number (if applicable)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: <input type="checkbox"/> Is a manufacturing schedule provided? <input type="checkbox"/> Is the schedule feasible to conduct an inspection within the review cycle?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	A manufacturing schedule is not provided.
DRUG SUBSTANCE INFORMATION					

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
6.	<p>Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?</p> <ul style="list-style-type: none"> <input type="checkbox"/> general information <input type="checkbox"/> manufacture <ul style="list-style-type: none"> <input type="checkbox"/> Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) <input type="checkbox"/> Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only <input type="checkbox"/> Includes complete description of product lots and their uses during development – BLA only <input type="checkbox"/> characterization of drug substance <input type="checkbox"/> control of drug substance <ul style="list-style-type: none"> <input type="checkbox"/> Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) <input type="checkbox"/> Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only <input type="checkbox"/> reference standards or materials <input type="checkbox"/> container closure system <input type="checkbox"/> stability <ul style="list-style-type: none"> <input type="checkbox"/> Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment 	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Information related to the drug substances is referred to DMFs.
DRUG PRODUCT INFORMATION					
7.	<p>Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?</p> <ul style="list-style-type: none"> <input type="checkbox"/> Description and Composition of the Drug Product <input type="checkbox"/> Pharmaceutical Development <ul style="list-style-type: none"> <input type="checkbox"/> Includes descriptions of changes in the manufacturing process from material used 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	<p style="margin-left: 20px;">in clinical to commercial production lots</p> <ul style="list-style-type: none"> ○ Includes complete description of product lots and their uses during development <p><input type="checkbox"/> Manufacture</p> <ul style="list-style-type: none"> ○ If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? <p><input type="checkbox"/> Control of Excipients</p> <p><input type="checkbox"/> Control of Drug Product</p> <ul style="list-style-type: none"> ○ Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Analytical validation package for release test procedures, including dissolution <p><input type="checkbox"/> Reference Standards or Materials</p> <p><input type="checkbox"/> Container Closure System</p> <ul style="list-style-type: none"> ○ Include data outlined in container closure guidance document <p><input type="checkbox"/> Stability</p> <ul style="list-style-type: none"> ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment <p><input type="checkbox"/> APPENDICES</p> <p><input type="checkbox"/> REGIONAL INFORMATION</p>				
BIOPHARMACEUTICS					
8.	<p>If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies:</p> <ul style="list-style-type: none"> • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided? 	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
9.	<p>Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product?</p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<p>The commercial formulation is the same as that used in the clinical studies. The Applicant will be recommended to develop an <i>in vitro</i> release test (IVRT)</p>

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	<i>(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)</i>				method and <i>in vitro</i> release acceptance criteria for the drug product to be used at release and during stability as a quality control parameter.
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Executed Batch Records for the drug substances are not available. CMC information of the drug substances is referred to DMFs.
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? <input type="checkbox"/> facilities and equipment <ul style="list-style-type: none"> <input type="checkbox"/> manufacturing flow; adjacent areas <input type="checkbox"/> other products in facility <input type="checkbox"/> equipment dedication, preparation, sterilization and storage <input type="checkbox"/> procedures and design features to prevent contamination and cross-contamination <input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> <input type="checkbox"/> avoidance and control procedures <input type="checkbox"/> cell line qualification <input type="checkbox"/> other materials of biological origin <input type="checkbox"/> viral testing of unprocessed bulk <input type="checkbox"/> viral clearance studies <input type="checkbox"/> testing at appropriate stages of production <input type="checkbox"/> novel excipients	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
17.	Are the following information available for Biotech Products: <input type="checkbox"/> Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example:	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS				
	<ul style="list-style-type: none">○ LAL instead of rabbit pyrogen○ Mycoplasma <p>Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples</p>			

Yichun Sun -A

Digitally signed by Yichun Sun -
A
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Yichun Sun -A,
0.9.2342.19200300.100.1.1=130
0393310
Date: 2015.02.05 14:53:25
-05'00'

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

/s/

MARY GRACE LUBAO
10/27/2015