

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-502

CHEMISTRY REVIEW(S)

NDA 21-502



Anthelios



**(Avobenzone, Ecamsule, and Octocrylene Topical Cream)
(avobenzone 2%, ecamsule 2%, and octocrylene 10%)**

L'Oreal USA Products, Inc.

**Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products**

Sue-Ching Lin

Review Chemist

**Office of New Drug Quality Assessment
Pre-Marketing Division II, Branch III**



Chemistry Review Data Sheet

1. NDA 21-502
2. REVIEW #: 2
3. REVIEW DATE: 05-July-2006
4. REVIEWER: Sue-Ching Lin
5. PREVIOUS DOCUMENTS:

Submissions Reviewed in Chemistry Review #1	Document Date
Original submission	12-May-2005
Amendment (BZ)	05-Aug-2005
Amendment (BC)	11-Jan-2006
Amendment (BC)	16-Feb-2006

6. SUBMISSION(S) BEING REVIEWED:

Subjects of this Review	Document Date
Resubmission (AZ)	18-May-2006
Amendment (BC)	12-Apr-2006
Amendment (BC)	22-Jun-2006

7. NAME & ADDRESS OF APPLICANT:

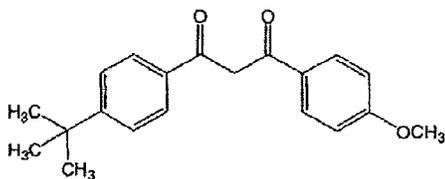
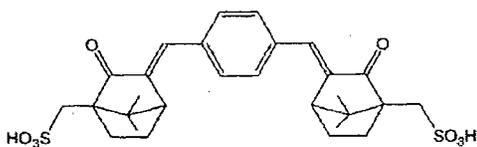
Name: L'Oreal USA Products, Inc.
Address: 111 L'Oreal Way
Clark, New Jersey 07066
Representative: Jean R. Grieve
Assistant Vice President, Drug Approval Group
Telephone: 732-680-5562

Chemistry Review Data Sheet

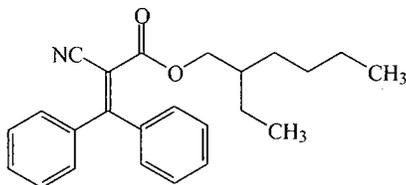
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Avobenzone

1-(p-tert-butylphenyl)-3-(p-methoxyphenyl)-1,3-propanedione

 $C_{20}H_{22}O_3$, MW 310.40, CAS 70356-09-1, other designation: Parsol[®] 1789**Ecamsule** (\pm) -(3E,3'E)-3,3'-(p-Phenylenedimethyldiylne)bis(2-oxo-10-bornanesulfonic acid) $C_{28}H_{34}O_8S_2$, MW 562.3, CAS 92761-26-7, other designation: Mexoryl[®] SX**Octocrylene**

2-Propenoic acid, 2-cyano-3,3-diphenyl, 2-ethylhexyl ester

 $C_{24}H_{27}NO_2$, MW 361.49, CAS 6197-30-4, Other designation: Uvinul[®] N539T

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	II	[Handwritten mark]	avobenzene	1	adequate	22-Feb-2006	
	II		avobenzene	1	adequate	16-Dec-2005	
	II		ecamsule	1	adequate	15-Feb-2006	
	II		octocrylene	1	adequate	17-Feb-2006	
	III			4	N/A		*
	III			4	N/A		*
	III			4	N/A		*
	III			4	N/A		*
	III			4	N/A		*
	III			4	N/A		*

* See page 53 of Chemistry Review #1 under container closure system for details

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

- 2 – Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under “Comments”)

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	59,126	SPF 15
NDA	[Handwritten mark]	
NDA		
NDA		



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	3/16/06	S. Adams
Pharm/Tox	N/A		
Clinical Pharmacology	N/A		
LNC	N/A		
Methods Validation	Not required per current ONDQA policy*		
Office of Drug Safety	Acceptable**	12/9/05	Tina Tezky, Michael Koenig**
EA	Categorical exclusion (see review)		
Microbiology	Approval	11/30/05	Stephen Langille

*The analytical procedures and their validations were reviewed and found to be adequate. Methods validation packages will not be sent to FDA laboratories because the methods do not meet the "method validation request criteria" according to the current ONDQA policy that was announced on 1/12/05.

**The proposed proprietary names were consulted to the Division of Medication Errors and Technical Support (DMETS) in the Office of Drug Safety (consults sent by Elaine Abraham, the Project Manager). The DMETS' 12/9/05 review states that DMETS does not recommend the use of the proprietary name [redacted] However, according to the 2/22/06 e-mail from Elaine Abraham (the project manager), DMETS gave the Office of Nonprescription Drugs (ONP) the option of going with the names or not, during a recent meeting between DMETS and ONP. The ONP's decision can be seen in the 2/21/06 labeling review by Dr. Michael Koenig, the ONP labeling reviewer, which indicates that all the proposed trade names are acceptable (see page 3 of the labeling review in DFS).



The Chemistry Review for NDA 21-502

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry review perspective, this NDA is recommended for approval.

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

None

II. Summary of Chemistry Assessments

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

(1) Drug Substances

The drug product contains three drug substances: avobenzone, ecamsule, and octocrylene. Avobenzone and octocrylene are active ingredients included in the over-the-counter (OTC) sunscreen monographs (21 CFR 352.10 and 352.20). These two drug substances are also USP monograph substances.

Ecamsule is a new molecular entity. It was included in the drug product in NDA —

□ ————— □ —————
→

Detailed information on the drug substances is referenced to their respective DMFs, which have been reviewed by this reviewer and found to be adequate to support this NDA.

Executive Summary Section

(2) Drug Product

The drug product is a sunscreen containing 2% of avobenzone, 2% of ecamsule, and 10% of octocrylene. The active ingredients were selected to provide a broad protection from UVA (320 to 400 nm) and UVB (290 to 320 nm) irradiation wavelengths. The absorption bands are as follows: avobenzone from 320 to 400 nm, octocrylene from 250 to 370 nm, and ecamsule from 290 to 400 nm.

The drug product also contains 17 excipients that provide functions such as

The drug product is packaged in a 100-mL tube with an _____ head and a _____ snap-top closure.

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

The drug product is intended to be applied topically for the prevention of sunburn due to sun exposure. It is proposed to be available over-the-counter. This topical formulation may be used on a daily basis as a moisturizer. It is to be applied evenly to skin before sun exposure. The formulation is not water-resistant and thus is not suitable for use in outdoor swimming.

The sunscreen is to be stored at 20-25°C. The submitted drug product stability data include long-term stability data for _____ months and accelerated stability data for 6 months on three primary stability batches manufactured at the proposed commercial manufacturing site. An expiration dating period of 30 months is granted for the drug product based on the stability data.



Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

As stated in the executive summary of chemistry review #1 of this NDA, the only pending CMC issue was the establishment inspection. This issue was resolved on March 16, 2006, when the Office of Compliance gave an "acceptable" recommendation for all the facilities used in the manufacture and control of the drug substance and drug product.

The applicant submitted an amendment on 4/12/06 proposing to add a conversion factor — in the calculation formula for the ecamsule impurities in the drug product impurity test [—] . The applicant later submitted the 6/22/06 amendment to eliminate the use of the conversion factor. Instead, a revised drug product specification was submitted with changes in the acceptance criteria for the ecamsule impurities. The revision appears to be acceptable, based on the historical toxicology/clinical batch data.

The CMC information regarding the drug substance and drug product is adequate to support the over-the-counter use of this drug product, a sunscreen.

III. Administrative

- A. **Reviewer's Signature** electronically signed in DFS
- B. **Endorsement Block** electronically signed in DFS
- C. **CC Block** electronically signed in DFS

2 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 142

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this page is the manifestation of the electronic signature.**

/s/

Sue Ching Lin
7/7/2006 02:36:22 PM
CHEMIST

Moo-Jhong Rhee
7/7/2006 02:54:07 PM
CHEMIST
Chief, Branch III

NDA 21-502

[-]

Anthelios

[-]

**(Avobenzone, Ecamsule, and Octocrylene Topical Cream)
(avobenzone 2%, ecamsule 2%, and octocrylene 10%)**

L'Oreal USA Products, Inc.

Sue-Ching Lin

Review Chemist

**Office of New Drug Quality Assessment
Pre-Marketing Division II, Branch III
for
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products**



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Chemistry Review Data Sheet

1. NDA 21-502
2. REVIEW #: 1
3. REVIEW DATE: 24-Feb-2006
4. REVIEWER: Sue-Ching Lin
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
End-of Phase 2 meeting (IND 59,126)	24-Jan-2001
Stability Matrix Design agreement	19-Apr-2001
Pre-NDA meeting	18-Sep-2001
Pre-NDA meeting follow-up	03-Dec-2001
FDA comments on viscosity presentation	04-Dec-2001
FDA fax providing comments on stability data	17-Jan-2002
Telecon discussing definition of cream and lotion	02-Apr-2002
FDA fax regarding CMC issues	13-Sep-2002

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original submission	12-May-2005
Amendment (BZ)	05-Aug-2005
Amendment (BC)	11-Jan-2006
Amendment (BC)	16-Feb-2006

7. NAME & ADDRESS OF APPLICANT:

Name: L'Oreal USA Products, Inc.
Address: 111 L'Oreal Way
Clark, New Jersey 07066
Representative: Jean R. Grieve
Assistant Vice President, Drug Approval Group
Telephone: 732-680-5562

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Names: The following - proprietary names were proposed (names in parentheses denote marketing division):

Anthelios (La Roche-Posay)

- b) Non-Proprietary Name: avobenzone, ecamsule, and octocrylene topical cream
 c) Code Name/# (ONDC only): _____ SPF 15 Daily Sunscreen, L'Oreal's internal formulation number 539-009
 d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1 (new molecular entity) NDA _____ 21-502)

- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: sunscreen

11. DOSAGE FORM: cream

12. STRENGTH/POTENCY: avobenzone 2%, ecamsule 2%, octocrylene 10%

13. ROUTE OF ADMINISTRATION: topical

14. Rx/OTC DISPENSED: ___ Rx x OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

___ SPOTS product - Form Completed

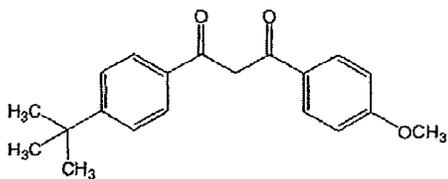
x Not a SPOTS product

Chemistry Review Data Sheet

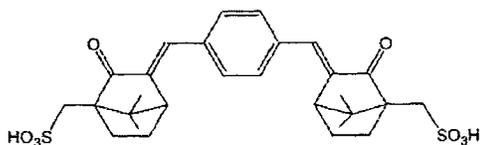
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Avobenzone

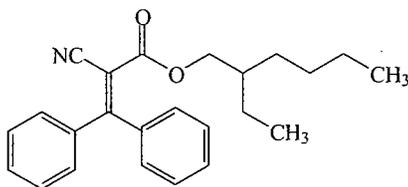
1-(p-tert-butylphenyl)-3-(p-methoxyphenyl)-1,3-propanedione

 $C_{20}H_{22}O_3$, MW 310.40, CAS 70356-09-1, other designation: Parsol[®] 1789**Ecamsule**

(±)-(3E,3'E)-3,3'-(p-Phenylenedimethylydyne)bis(2-oxo-10-bornanesulfonic acid)

 $C_{28}H_{34}O_8S_2$, MW 562.3, CAS 92761-26-7, other designation: Mexoryl[®] SX**Octocrylene**

2-Propenoic acid, 2-cyano-3,3-diphenyl, 2-ethylhexyl ester

 $C_{24}H_{27}NO_2$, MW 361.49, CAS 6197-30-4, Other designation: Uvinul[®] N539T

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
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	II		avobenzone	1	adequate	16-Dec-2005	
	II		ecamsule	1	adequate	15-Feb-2006	
	II		octocrylene	1	adequate	17-Feb-2006	
	III			4	N/A		*
	III			4	N/A		*
	III			4	N/A		*
	III			4	N/A		*
	III			4	N/A		*
	III			4	N/A		*

*See page 53 of this review under container closure system for details

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under “Comments”)

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	59,126	SPF 15
NDA		
NDA		
NDA		



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending*		
Pharm/Tox	N/A		
Clinical Pharmacology	N/A		
LNC	N/A		
Methods Validation	Not required per current ONDQA policy**		
Office of Drug Safety	Acceptable***	12/9/05	Tina Tezky, Michael Koenig**
EA	Categorical exclusion (see review)		
Microbiology	Approval	11/30/05	Stephen Langille

* All the manufacturing and control facilities are acceptable, with the exception of [redacted] (the new avobenzone manufacturing site). The inspection of [redacted] is scheduled for March 13-16, 2006 (the due date of this NDA is March 10, 2006).

**The analytical procedures and their validations were reviewed and found to be adequate. Methods validation packages will not be sent to FDA laboratories because the methods do not meet the "method validation request criteria" according to the current ONDQA policy that was announced on 1/12/05.

***The proposed proprietary names were consulted to the Division of Medication Errors and Technical Support (DMETS) in the Office of Drug Safety (consults sent by Elaine Abraham, the Project Manager). At the completion of this CMC review, only the review of [redacted] by DMETS is in DFS (the consults for the remaining proprietary names were sent separately). The DMETS' 12/9/05 review states that DMETS does not recommend the use of the proprietary name [redacted] is [redacted]. However, according to the 2/22/06 e-mail from Elaine Abraham, DMETS gave the Office of Nonprescription Drugs (ONP) the option of going with the names or not, during a recent meeting between DMETS and ONP. The ONP's decision can be seen in the 2/21/06 labeling review by Dr. Michael Koenig, the ONP labeling reviewer, which indicates that all the proposed trade names are acceptable (see page 3 of the labeling review).

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On Original**



The Chemistry Review for NDA 21-502

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry review perspective, this NDA is approvable pending an acceptable recommendation from the Office of Compliance for the establishment inspections. As of this review, the inspection at C ~ D facility is still pending.

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

None

II. Summary of Chemistry Assessments

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

(1) Drug Substances

The drug product contains three drug substances: avobenzone, ecamsule, and octocrylene. Avobenzone and octocrylene are active ingredients included in the over-the-counter (OTC) sunscreen monographs (21 CFR 352.10 and 352.20). These two drug substances are also USP monograph substances.

Ecamsule is a new molecular entity. It was included in the drug product in NDA C ~

Detailed information on the drug substances is referenced to their respective DMFs, which have been reviewed by this reviewer and found to be adequate to support this NDA.

Executive Summary Section

(2) Drug Product

The drug product is a sunscreen containing 2% of avobenzone, 2% of ecamsule, and 10% of octocrylene. The active ingredients were selected to provide a broad protection from UVA (320 to 400 nm) and UVB (290 to 320 nm) irradiation wavelengths. The absorption bands are as follows: avobenzone from 320 to 400 nm, octocrylene from 250 to 370 nm, and ecamsule from 290 to 400 nm.

The drug product also contains 17 excipients that provide functions such as

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The drug product is packaged in a 100-mL tube with an head and a snap-top closure.

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

The drug product is intended to be applied topically for the prevention of sunburn due to sun exposure. It is proposed to be available over-the-counter. This topical formulation may be used on a daily basis as a moisturizer. It is to be applied evenly before sun exposure. The formulation is not water-resistant and thus is not suitable for use in outdoor swimming.

The sunscreen is to be stored at 20-25°C. The submitted drug product stability data include long-term stability data for months and accelerated stability data for 6 months on three primary stability batches manufactured at the proposed commercial manufacturing site. An expiration dating period of 30 months is granted for the drug product based on the stability data.

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

The CMC information regarding the drug substance and drug product is adequate to support the over-the-counter use of this drug product, a sunscreen. The only pending issue is the establishment inspection.

The inspection of [redacted], which is one of the avobenzone drug substance manufacturing sites, is still pending. This NDA can not be approved without an “acceptable” recommendation from the Office of Compliance for all the manufacturing and control facilities.

[redacted] proprietary names are proposed in the NDA. The Office of Drug Safety has objections to the use of [redacted]; one of the proposed names, because it is [redacted]. However, the Office of Non-prescription Drugs (ONP) has determined that all of the proposed proprietary names are acceptable. Refer to the 2/21/06 labeling review by the ONP reviewer Dr. Michael Koenig.

III. Administrative

- A. Reviewer’s Signature** electronically signed in DFS
- B. Endorsement Block** electronically signed in DFS
- C. CC Block** electronically signed in DFS

57 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process

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/s/

Sue Ching Lin
3/2/2006 04:43:49 PM
CHEMIST

Moo-Jhong Rhee
3/2/2006 04:55:35 PM
CHEMIST
Chief, Branch III

NDA FILEABILITY CHECKLIST

NDA Number: 21-502 Applicant: L'Oreal USA Products, Inc. Stamp Date: 5/12/05

Drug Name: avobenzone, ecamsule, and octocrylene topical lotion

IS THE CMC SECTION OF THE APPLICATION FILABLE? Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	√		Volume 1, page 5, Form 356h Volume 3, pages 19-21 for drug substance Volume 3, page 121 for drug product Information regarding _____ facility was provided on 7/1/05 by e-mail.
5	Is a statement provided that all facilities are ready for GMP inspection?	√		Volume 1, page 5, Form 356h
6	Has an environmental assessment report or categorical exclusion been provided?	√		Volume 4, page 325, categorical exclusion
7	Does the section contain controls for the drug substance?	√		Volume 3, pages 28-102
8	Does the section contain controls for the drug product?	√		Volume 3, pages 193-305
9	Has stability data and analysis been provided to support the requested expiration date?	√		Volume 4, pages 306-320 and Volume 5, pages 127-231. _____ month long-term data and 6-month accelerated data on 3 full production batches to support a _____ month expiration period.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
11	Have draft container labels been provided?	√		Volume 1, pages 137-378 There are _____ proprietary names as shown on page 008 of Volume 2.
12	Has the draft package insert been provided?		√	It is stated in Volume 2, page 8 that no package insert is planned.
13	Has an investigational formulations section been provided?	√		Volume 4, pages 321-324
14	Is there a Methods Validation package?	√		Volumes 7 & 8
15	Is a separate microbiological section included?			N/A

If the NDA is not fileable from a manufacturing and controls perspective state why it is not.

Reviewing Chemist: Sue-Ching Lin

Date: 7/5/05

Team Leader: John Smith, Ph.D.

Date:

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

/s/

Sue Ching Lin
7/5/05 05:22:27 PM
CHEMIST

John Smith
7/8/05 04:59:12 PM
CHEMIST