

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-471

CHEMISTRY REVIEW(S)



NDA 21-471

**Anthelios 20
Capital Soleil 20
UV Expert 20
UV Protective Suncare**

**(Avobenzone, Ecamsule, Octocrylene, and Titanium Dioxide Topical Cream)
(Avobenzone 2%, Ecamsule 2%, Octocrylene 10%, and Titanium Dioxide 2%)**

L'Oreal USA Products, Inc.

**Jane L. Chang, Ph.D.
Chemistry Reviewer**

**Office of New Drug Quality Assessment
Pre-Marketing Division II, Branch III
for
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
(HFD-560)**

Chemistry Review Data Sheet

1. NDA 21-471
2. REVIEW #: 2
3. REVIEW DATE: 14-Sep-2006
4. REVIEWER: Jane L. Chang, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original submission	27-Sep-2005
Amendment (BC)	22-Nov-2005
Amendment (BC)	11-Jan-2006
Amendment (BC)	17-Feb-2006
Amendment (BC)	13-Apr-2006
Amendment (BC)	12-May-2006
Amendment (BC)	12-Jun-2006
Amendment (BC)	19-Jun-2006

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (BC)	04-Aug-2006
Amendment (AL)*	08-Aug-2006

*CMC reviewers are not required to review labeling for OTC NDA per ONDQA policy as stated in the 4/27/06 email.

**CHEMISTRY REVIEW**

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	L'Oreal USA Products, Inc.
Address:	30 Terminal Avenue Clark, NJ 07066
Representative:	Jean R. Grieve Assistant Vice President
Telephone:	732-680-5562

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: The following 4 proprietary names were proposed (names in parentheses denote marketing division):

- Anthelios 20 (La Roche-Posay)
- Capital Soleil 20 (Vicky)
- UV Expert 20 (Lancôme)
- UV Protective Suncare (Kiehl's)

b) Non-Proprietary Name (USAN): avobenzone, ecamsule, octocrylene, and titanium dioxide topical cream

c) Code Name/# (ONDQA only): ~~_____~~ SPF 20 Water Resistant, L'Oreal's internal formulation number 539-106

d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 4 (new combination) and 5 (new formulation)
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Combination of four sunscreen active ingredients for the prevention of sunburn: ~~_____~~ following ~~_____~~ exposure to ultraviolet radiation (UVR)

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: Ecamsule 2%, Avobenzone 2%, Octocrylene 10%, Titanium Dioxide 2%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: Rx OTC

CHEMISTRY REVIEW

Chemistry Review Data Sheet

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

_____ SPOTS product – Form Completed

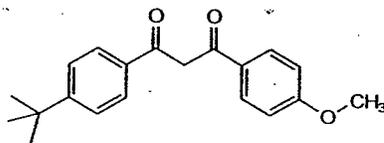
___ X ___ Not a SPOTS product

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

This drug product contains four drug substances (trade names are in parentheses): ecamsule (Mexoryl® SX), avobenzene (Parsol® 1789), octocrylene _____ and titanium dioxide.

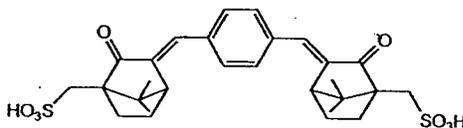
Avobenzene, USP

_____ Avobenzene is an Over-The-Counter (OTC) sunscreen, covered by 21 CFR 352.20(a)(2).



1-(*p*-*tert*-butylphenyl)-3-(*p*-methoxyphenyl)-1,3-propanedione
CAS number: 70356-09-1 C₂₀H₂₂O₃ MW = 310.40 g/mole

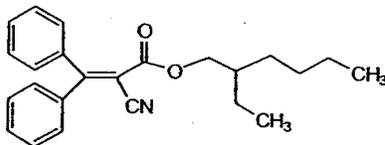
Ecamsule



(±)(3E,3'E)-3,3'-(*p*-phenylenedimethyldiylidene)bis(2-oxo-10-bornanesulfonic acid)
CAS number: 92761-26-7 C₂₈H₃₄O₈S₂ MW = 562.69 g/mole

Octocrylene, USP

Octocrylene is an OTC sunscreen, covered by 21 CFR 352.20(a)(1) and 352.20(a)(2).



2-ethylhexyl 2-cyano-3,3-diphenylacrylate
CAS number: 6197-30-4 C₂₄H₂₇NO₂ MW = 361.48 g/mol

Titanium Dioxide, USP

Titanium dioxide is an OTC sunscreen, covered by 21 CFR 352.20(a)(1).



CAS number: 13463-67-7 TiO₂ MW = 79.87 g/mole

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
1				3	adequate	17-Feb-2006	
				3	adequate	01-Mar-2006	
				3	adequate	16-Dec-2005	
				3	adequate	15-Feb-2006	
				4	N/A		
				4	N/A		**
				4	N/A		**
				4	N/A		**

*Formerly known as

**The container closure system is identical to NDA 21-501. The review by Sue-Ching Lin (3/2/06) found it acceptable. See NDA 21-501 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 I 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)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	59,126	SPF 15 W/R
NDA	21-501	SPF 15 Water Resistant Cream
NDA	21-502	SPF 15 Daily Sunscreen Cream

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	3/29/2006	S. Adams
Pharm/Tox	N/A		
Biopharm	N/A		
Methods Validation	N/A per current ONDQA policy*		
Office of Drug Safety	Acceptable**	2/14/2006 3/8/2006 3/9/2006 7/25/2006	L. Wisniewski F. Duffy T. Tezky M. Koenig
EA	Categorical exclusion (see review)		
Microbiology	Approval	11/29/2005	Stephen Langille, Ph.D.

*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' reviews states that DMETS does not recommend the use of the proprietary names Anthelios, Solar Expertise, and UV Expert. DMETS does not have objection for the use of "Capital Soleil 20", but revisions are recommended. 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 labeling review indicated that all of the proposed trade names are acceptable. See the Labeling review by M. Koenig on July 25, 2006.

**APPEARS THIS WAY
ON ORIGINAL**



The Chemistry Review for NDA 21-471

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry, manufacturing, and controls 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)

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Executive Summary Section

Drug Substances

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 and _____ following _____ exposure to ultraviolet radiation. It is proposed to be distributed via over-the-counter. The drug-product is to be applied liberally 15 minutes before sun exposure and reapply as needed or after towel drying, swimming, or perspiring.

The sunscreen cream is to be stored at 20-25 °C (68-77 °F). When stored under the specified conditions, the drug product has an expiration dating period of _____

C. Basis for Approvability or Not-Approval Recommendation

As stated in the executive summary of CMC review #1, adequate data have been submitted to ensure the drug product's identity, strength, quality, purity, potency, and stability as a sunscreen product for over-the-counter use.

An amendment on August 4, 2006 stated that the titanium dioxide used for this NDA is not _____ material. The typical _____ of titanium dioxide is greater than _____ and less than _____

From a CMC standpoint, this new drug application may be approved.

III. Administrative

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



CHEMISTRY REVIEW



Executive Summary Section

Chemistry Assessment

The NDA was issued an "approvable" letter on July 25, 2006 due to deficiencies in labeling. There was no CMC issue as stated in the executive summary of chemistry review #1 of this NDA. A resubmission for labeling (AL) was submitted on August 8, 2006. CMC reviewers are not required to review labeling for OTC NDA per ONDQA policy as stated in the 4/27/06 email. Changes in the trade names in the August 8, 2006 amendment is summarized below:

Trade names proposed in the Original submission	Trade names proposed in the 8/8/2006 Amendment (AL)
Anthelios (La Roche-Posay)	Anthelios 20 (La Roche-Posay)
Capital Soleil (Vicky)	Capital Soleil 20 (Vicky)
Solar Expertise (L'Oreal)	UV Protective Suncare (Kiehl's)
UV Expert (Lancôme)	UV Expert 20 (Lancôme)

The Chemistry Classification Code is changed from Types 1 (new molecular entity) and 4 (new combination) in review #1 to Types 4 and 5 (new formulation) in this review. This change is due to the approval of NDA 21-502 on July 21, 2006, which includes ecamsule as one of the three drug substances. Thus, ecamsule is not a new molecular entity for NDA 21-471.

The applicant submitted a minor chemistry amendment (BC) on August 4, 2006 to address a telephone inquiry by the Project Manager, E. Abraham. The question was:

Is the titanium dioxide, USP utilized in this formulation _____ material?

The applicant responded that the titanium dioxide used for this NDA is not _____ material. It is _____ material. The product specification sheet dated May 1997, from the supplier, _____, indicates that the typical _____ maximum and _____ average. The Material Safety Data Sheet (MSDS) for _____ Titanium Dioxide, All Grades, Dry Product was also provided, which indicates that primary _____ greater than _____. In the Section 8 of the MSDS, additional description regarding _____ is provided and listed below:

Reviewer's Assessment: The general definition of _____
 _____ . Based on the information provided, the titanium dioxide, USP, used in this NDA is not
 _____ The response is acceptable.

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

/s/

Jane Chang
9/14/2006 10:12:56 AM
CHEMIST

Moo-Jhong Rhee
9/14/2006 11:51:49 AM
CHEMIST
Chief, Branch III

NDA 21-471

**Anthelios
Capital Soleil
Solar Expertise
UV Expert**

**(Avobenzone, Ecamsule, Octocrylene, and Titanium Dioxide Topical Cream)
(Avobenzone 2%, Ecamsule 2%, Octocrylene 10%, and Titanium Dioxide 2%)**

L'Oreal USA Products, Inc.

Jane L. Chang, Ph.D.

Chemistry Reviewer

**Office of New Drug Quality Assessment
Pre-Marketing Division II, Branch III
for
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
(HFD-560)**

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Chemistry Review Data Sheet

1. NDA 21-471
2. REVIEW #: 1
3. REVIEW DATE: 20-Jun-2006
4. REVIEWER: Jane L. Chang, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
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 for Pre-NDA Meeting and stability data Follow-up	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:

Submission(s) Reviewed	Document Date
Original submission	27-Sep-2005
Amendment (BC)	22-Nov-2005
Amendment (BC)	11-Jan-2006
Amendment (BC)	17-Feb-2006
Amendment (BC)	13-Apr-2006
Amendment (BC)	12-May-2006
Amendment (BC)	12-Jun-2006
Amendment (BC)	19-Jun-2006

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	L'Oreal USA Products, Inc.
Address:	30 Terminal Avenue Clark, NJ 07066
Representative:	Jean R. Grieve Assistant Vice President
Telephone:	732-680-5562

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: The following 4 proprietary names were proposed (names in parentheses denote marketing division):

- Anthelios (La Roche-Posay)
- Capital Soleil (Vicky)
- Solar Expertise (L'Oreal)
- UV Expert (Lancôme)

b) Non-Proprietary Name (USAN): avobenzone, ecamsule, octocrylene, and titanium dioxide topical cream

c) Code Name/# (ONDQA only): _____ SPF 20 Water Resistant, L'Oreal's internal formulation number 539-106

d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1 (new molecular entity), 4 (new combination)
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Combination of four sunscreen active ingredients for the prevention of sunburn and _____ following _____ exposure to ultraviolet radiation (UVR)

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: Ecamsule 2%, Avobenzone 2%, Octocrylene 10%, Titanium Dioxide 2%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: ___ Rx ___ X ___ OTC

CHEMISTRY REVIEW

Chemistry Review Data Sheet

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 _____ SPOTS product – Form Completed

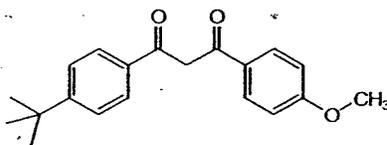
_____ X Not a SPOTS product

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

This drug product contains four drug substances (trade names are in parentheses): ecamsule (Mexoryl® SX), avobenzone (Parsol® 1789), octocrylene _____, and titanium dioxide.

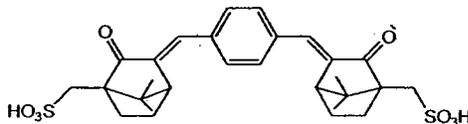
Avobenzone, USP

_____ Avobenzone is an Over-The-Counter (OTC) sunscreen, covered by 21 CFR 352.20(a)(2).



1-(*p*-*tert*-butylphenyl)-3-(*p*-methoxyphenyl)-1,3-propanedione
 CAS number: 70356-09-1 C₂₀H₂₂O₃ MW = 310.40 g/mole

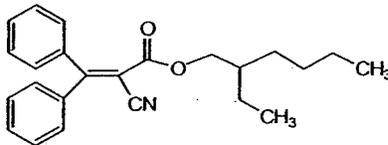
Ecamsule



(±)(3E,3'E)-3,3'-(*p*-phenylenedimethylidene)bis(2-oxo-10-bornanesulfonic acid)
 CAS number: 92761-26-7 C₂₈H₃₄O₈S₂ MW = 562.69 g/mole

Octocrylene, USP

Octocrylene is an OTC sunscreen, covered by 21 CFR 352.20(a)(1) and 352.20(a)(2).



2-ethylhexyl 2-cyano-3,3-diphenylacrylate
 CAS number: 6197-30-4 C₂₄H₂₇NO₂ MW = 361.48 g/mol

Titanium Dioxide, USP

Titanium dioxide is an OTC sunscreen, covered by 21 CFR 352.20(a)(1).



CAS number: 13463-67-7 TiO₂ MW = 79.87 g/mole

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
┌				3	adequate	17-Feb-2006	
				3	adequate	01-Mar-2006	
				3	adequate	16-Dec-2005	
				3	adequate	15-Feb-2006	
				4	N/A		
				4	N/A		**
				4	N/A		**
				4	N/A		**

*Formerly known as _____

**The container closure system is identical to NDA 21-501. The review by Sue-Ching Lin (3/2/06) found it acceptable. See NDA 21-501 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)

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	59,126	SPF 15 W/R
NDA	21-501	SPF 15 Water Resistant Cream
NDA	21-502	SPF 15 Daily Sunscreen Cream

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	3/29/2006	S. Adams
Pharm/Tox	N/A		
Biopharm	N/A		
Methods Validation	N/A per current ONDQA policy*		
Office of Drug Safety	Not recommended**	2/14/2006 3/8/2006 3/9/2006	L. Wisniewski F. Duffy T. Tezky
EA	Categorical exclusion (see review)		
Microbiology	Approval	11/29/2005	Stephen Langille, Ph.D.

*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' reviews states that DMETS does not recommend the use of the proprietary name Anthelios, Solar Expertise, and UV Expert. DMETS does not have objection for the use of Capital Soleil 20, but revisions are recommended. 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. At the completion of this CMC review, ONP labeling review has not been completed yet.

The Chemistry Review for NDA 21-471

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry, manufacturing, and controls review perspective, this NDA may be approved.

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)

Executive Summary Section

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 and _____ following _____ exposure to ultraviolet radiation. It is proposed to be distributed via over-the-counter. The drug product is to be applied liberally 15 minutes before sun exposure and reapply as needed or after towel drying, swimming, or perspiring.

The sunscreen cream is to be stored at 20-25 °C (68-77 °F). When stored under the specified conditions, the drug product has an expiration dating period of _____

C. Basis for Approvability or Not-Approval Recommendation

Adequate data have been submitted to ensure the drug product's identity, strength, quality, purity, potency, and stability as a sunscreen product for over-the-counter use. Therefore, from a CMC standpoint, this new drug application may be approved.

III. Administrative

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

55 Page(s) Withheld

X Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

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

/s/

Jane Chang
6/30/2006 03:31:31 PM
CHEMIST

Moo-Jhong Rhee
6/30/2006 03:34:42 PM
CHEMIST
Chief, Branch III