

Appendix A: Prescription Study Results for UV Expert

Requisition 1	Requisition 2	Verbal
UV expert	UV Expera	UV Expert
UV Expert	UV Expera	UV Expert
UV Expert	UV Expera	UV Expert
UV Expert	UV Expert	UV Expert
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UV Expert	UV Expira	
UV Expert	UV Expua	

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/s/

Felicia Duffy
3/8/2006 10:15:07 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
3/8/2006 01:20:10 PM
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Carol Holquist
3/8/2006 02:01:23 PM
DRUG SAFETY OFFICE REVIEWER

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(WO22; Mail Stop 4447)

DATE RECEIVED:

January 15, 2006

DATE OF DOCUMENT:

September 27, 2005

DESIRED COMPLETION DATE:

May 15, 2006

PDUFA DATE:

July 28, 2006

ODS CONSULT #: 06-0044

TO: Andrea Leonard-Segal, M.D., Acting Director
Division of Nonprescription Clinical Evaluation, HFD-560

THROUGH: Alina R. Mahmud, RPh, MS, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Tina M. Tezky, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME:

Solar Expertise

(Avobenzone 2%, Ecamsule 2%, Octocrylene 10%, Titanium Dioxide 2% Lotion)

NDA SPONSOR:

L'Oreal USA Products

NDA#: 21-471

RECOMMENDATIONS:

1. Although we have not identified any proprietary or established names that would render the name "Solar Expertise" objectionable from a look-alike or sound-alike perspective, DMETS is concerned with the use of "Expertise" in the proprietary name. We believe "Expertise" is promotional and question what it communicates to consumers (see section III of this review). For these reasons, DMETS does not recommend the use of the proprietary name Solar Expertise. However, if Solar Expertise is approved, we recommend relocating the SPF rating to appear immediately following the statement of identity in order to increase prominence and clearly differentiate this formulation from future formulations (e.g., Solar Expertise Sunscreen Lotion SPF 20).

This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.
3. Because DDMAC does not have regulatory authority to review proposed OTC proprietary names, they did not comment on the name UV Expert.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-796-0538.

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
WO22; Mail Stop 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: February 22, 2006

NDA#: 21-471

NAME OF DRUG: **Solar Expertise**
(Avobenzone 2%, Ecamsule 3%, Octocrylene 10%, Titanium Dioxide 2% Lotion)

NDA HOLDER: L'Oreal USA Products

I. INTRODUCTION:

This consult was written in response to a request from the Division of Nonprescription Clinical Evaluation (HFD-560) for a review of the proprietary name, "Solar Expertise", regarding potential name confusion with other proprietary and/or established drug names. Container labels, carton and insert labeling were provided for review and comment.

The proprietary name, Solar Expertise, was previously reviewed on December 9, 2005 (ODS consult #: 05-0173 and 05-0174). Solar Expertise is an extension of the Solar Expertise sunscreen product line by L'Oreal that is currently marketed in Europe. The two previously reviewed formulations of Solar Expertise (NDA 21-501 and NDA 21-502) are pending approval. At the time of the original review we did not identify any proprietary or established names that would render the name "Solar Expertise" objectionable from a look-alike or sound-alike perspective. However, DMETS was concerned with the use of "Expertise" in the proprietary name. We believe "Expertise" is promotional and question what it communicates to consumers. For those reasons, DMETS did not recommend the use of the proprietary name Solar Expertise. Subsequent to this review, DMETS was informed by the Division of Nonprescription Clinical Evaluation that the current practice, of naming OTC sunscreens, is to use the same proprietary name and distinguish them by using descriptors and/or the SPF number. Although DMETS does not recommend the use of the same proprietary name for products that contain different active ingredients for prescription products, we acknowledge that there is precedent for this naming convention with sunscreens in the Division of Nonprescription Clinical Evaluation. We note that the sponsor prominently displays the SPF rating on the principal display panel of each label. If the Division allows the use of the proprietary name Solar Expertise, DMETS recommends that the sponsor relocate the SPF rating on the principal display panel of the label to appear immediately following the statement of identity in order for the user to adequately differentiate this formulation from future formulations (e.g., Solar Expertise Sunscreen Lotion SPF 20).

PRODUCT INFORMATION

Solar Expertise is an over-the-counter (OTC) product that contains four ultraviolet radiation (UVR) filters providing protection throughout the ultraviolet B (UVB) and ultraviolet A (UVA) spectrum. These active ingredients include ecamsule, avobenzone, octocrylene, and titanium dioxide. Solar Expertise is indicated for the prevention of sunburn and is to be applied evenly to cleansed skin before sun exposure and as needed. Solar Expertise is for external use only. Solar Expertise will be supplied in 100 mL tubes.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to Solar Expertise to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁴. The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Solar Expertise. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. Because over-the-counter drug products are regulated by the FTC, DDMAC is unable to provide comments on the proposed trade name Solar Expertise.
2. Since the August 2005 proprietary name review, the Expert Panel has not identified additional proprietary names that were thought to have the potential for confusion with Solar Expertise. This product and the two previously reviewed formulations are listed in Table 1 (see below), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel.

Product Name	Established name, Dosage form(s)	Usual adult dose	Other
Solar Expertise OTC	Sunscreen Lotion SPF 20/PFA18 Ecamsule 2%, Avobenzone 2%, Octocrylene 10%, Titanium Dioxide 2%	Apply liberally 15 minutes before sun exposure and reapply as needed	
Solar Expertise*** OTC (NDA 21-501)	Sunscreen Lotion SPF15/PFA21 Ecamsule 3%, Avobenzone 2%, Octocrylene 10%	Apply liberally 15 minutes before sun exposure. Reapply as needed or after towel drying, swimming, or perspiring.	LA/SA
Solar Expertise*** OTC (NDA 21-502)	Sunscreen Lotion for Face SPF15/PFA15 Ecamsule 2%, Avobenzone 2%, Octocrylene 10%	Apply evenly to cleansed skin before sun exposure and as needed.	LA/SA
*Frequently used, not all-inclusive. **LA (look-alike), SA (sound-alike) ***Name pending approval. Not FOI releasable.			

¹ MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], Drugs@FDA, the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁵ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Solar Expertise were discussed by the Expert Panel.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Solar Expertise, no additional concerns related to look-alike and/or sound-alike confusion were found since our August 2005 review. Our concerns remain with the use of the modifier "Expertise". Additionally, we have concerns with the differentiation of Solar Expertise products that contain different active ingredients.

1. Nomenclature Concerns with "Expertise"

DMETS is concerned with the use of the modifier "Expertise" in the proprietary name. We note the sponsor, L'Oreal, uses this term with their cosmetic product line (e.g. Dermo Expertise) and acknowledge there does not appear to be any safety concerns with the use of this modifier for this product, but consider it promotional. The term "expertise" has not been used in conjunction with any approved prescription drug product, and thus this may set or establish precedence for other approved drug products. We question what "Expertise" communicates to consumers. Additionally, although DDMAC does not have regulatory authority to review proposed OTC proprietary names, they feel the name has promotional implications as well. Thus, we do not recommend the use of the proprietary name, Solar Expertise. Although it is noted that there are no safety concerns with the use of the modifier "Expertise", DMETS is concerned that this may establish a precedence for the use of this modifier in future products. Thus, we ask the sponsor to reconsider the use of this modifier.

2. Differentiation of Solar Expertise products that Contain Different Active Ingredients

We note that the sponsor proposes to market three products containing two different sets of active ingredients (avobenzone, ecamsule, octocrylene vs. avobenzone, ecamsule, octocrylene, titanium dioxide) with the same proprietary name, Solar Expertise. This is concerning because consumers would not know by the name alone that there are different active ingredients in each. If a consumer is allergic to a specific ingredient they may not realize that the active ingredients of Solar Expertise may be different depending upon the SPF they choose. However, DMETS recognizes that the current practice, of naming OTC sunscreens, is to use the same proprietary name and distinguish them by using descriptors and/or the SPF number. Although DMETS does not recommend the use of the same proprietary name for products that contain different active ingredients for prescription products, we acknowledge that there is precedent for this naming convention with sunscreens in the Division of Nonprescription Clinical Evaluation.

III. COMMENTS TO THE SPONSOR

DMETS does not recommend the use of the proprietary name Solar Expertise due to nomenclature concerns with the name "Expertise".

- A. DMETS is concerned with the use of the modifier "Expertise" in the proprietary name. We note the sponsor, L'Oreal, uses this term with their cosmetic product line (e.g. Dermo Expertise) and acknowledge there does not appear to be any safety concerns with the use of this modifier for this product, but consider it promotional. The term "expertise" has not been used in conjunction with any approved prescription drug product, and thus this may set or establish precedence for other approved drug products. We question what "Expertise" communicates to consumers. Additionally, although DDMAC does not have regulatory authority to review proposed OTC proprietary names, they feel the name has promotional implications as well. Thus, we do not recommend the use of the proprietary name, Solar Expertise. DDMAC could not comment on the proprietary name Solar Expertise because they do not have regulatory authority to review proposed OTC proprietary names. Although it is noted that there are no safety concerns with the use of the modifier "Expertise", DMETS is concerned that this may establish a precedence for the use of this modifier in future products. Thus, we ask the sponsor to reconsider the use of this modifier.

In the review of the container labels, carton and insert labeling of Solar Expertise, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

B. GENERAL COMMENTS

1. Present the entire proprietary name (Solar Expertise) in the same type and size font.
2. Sun Protection Factor (SPF) is a recognized abbreviation on U.S. marketed sunscreens. However, the sponsor also uses PFA to indicate "Protection Factor UVA." DMETS questions whether this is a recognized term currently used and whether patients are aware of its meaning. If PFA is not recognized by users, then DMETS recommends deleting this term from the labels and labeling. If PFA is allowed, then the sponsor should use an asterisk (*) on the principal display panel to refer user to the back panel where PFA is defined.
3. Relocate the SPF rating to appear immediately following the statement of identity (e.g., Solar Expertise Sunscreen Lotion SPF 20).
4. DMETS notes that the term 'MexorylTM SX' is a trademark for Ecamsule and the term 'Parsol®' is a trademark for Avobenzone. Since the active ingredients, Ecamsule and Avobenzone, must be listed as part of the established name and active ingredients, delete all references to 'MexorylTM SX and Parsol®, as they may be a source of confusion to patients who may think that this is a fourth or fifth active ingredient in the product.
5. Eliminate terminal zeros in the expression of strength and volume throughout labels and labeling. DMETS notes several incidents where a terminal zero is used in expression of the strength. The use of terminal zeros may result in error as often the decimals are overlooked. As evidenced by our post-marketing surveillance, the use of terminal zeros could potentially result in a ten-fold medication dose error. Although it is unlikely that a ten-fold dosing error would occur in this instance, the use of terminal zeros in the expression of strength or volume is not in accordance with the General Notice (page 10) of the 2004 USP, which states, '...to help minimize the possibility of error in the dispensing of administration of drugs...the quantity of active ingredients when expressed in whole numbers shall be shown without a decimal point that is followed by a

terminal zero.” In addition, the use of terminal zeros is specially listed as a dangerous abbreviation, acronym, or symbol in the 2006 National patient Safety Goals of the Joint Commission of Accreditation of Healthcare Organizations (JCAHO). Lastly, safety groups such as ISMP also list terminal zeros on their dangerous abbreviations and dose designations list.

C. CONTAINER LABEL (Main Display Panel)

Include a statement of identity on the primary display panel to be in accordance with 21 CFR 201.61. ‘The principal display panel of an over-the-counter drug in package form shall bear as one of its principal features a statement of the identity of the commodity. Such statement of identity shall be in terms of the established name of the drug, if any there be, followed by an accurate statement of the general pharmacological category (ies) of the drug or the principal intended action (s) of the drug....The statement of identity shall be presented in bold face type on the principal display panel, shall be in a size reasonably related to the most prominent printed matter on such panel, and shall be in lines generally parallel to the base on which the package rests as it is designed to be displayed....’

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/s/

Tina Tezky
3/8/2006 10:40:36 AM
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Denise Toyer
3/8/2006 01:28:04 PM
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Carol Holquist
3/8/2006 02:04:12 PM
DRUG SAFETY OFFICE REVIEWER

RECORD OF TELECONFERENCE

Date: January 23, 2006
Project Manager: Elaine Abraham
Subject: Discuss chemistry issues
NDA: 21-501, 21-502, 21-471
Sponsor: L'Oreal
Product Name: SPF-15 and SPF-20 Sunscreens
Phone No: (732) 680-5562

FDA participants: Moo Jhong Rhee, Ph.D., Branch Chief
Shulin Ding, Ph.D., Pharmaceutical Assessment Lead
Sue-Ching Lin, M.S., R.Ph., Chemistry Reviewer
Jane Chang, Ph.D., Chemistry Reviewer
Elaine Abraham, RPM

L'Oreal participants: Jean Grieve, Assistant VP, R&D, Drug Approval Group
Henry Kalinoski, Ph.D., Director, Product Site Support Analytical
Chemistry & Microbiology, R & D

Background: L'Oreal submitted NDAs 21-501 and 21-502 in May 2005 for a 3-ingredient combination sunscreen product. NDA 21-471 was submitted in September 2005 for a 4-ingredient combination sunscreen. Chemistry issues are similar for the three NDAs. This discussion was part of an on-going back and forth between FDA and L'Oreal to resolve outstanding chemistry issues.

Discussion: The following issues and information requests were discussed:

1. FDA has received a sample of the drug product for each NDA. These samples do not appear to be lotions (refer to *International Journal of Pharmaceutics* 295 (2005) 101-112, which was sent to the applicant). This article represents the FDA's current thinking on classification of dosage forms for topical drugs. A lotion is a liquid dosage form, which is pourable and flows; and conforms to its container at room temperature. These samples appear to be creams, rather than pourable liquids.

L'Oreal referred to the flow chart on page 109 of the article and said their product is pourable and conforms to the container at room temperature. The footnote states that a semisolid does not conform to the container at room temperature.

FDA stated that the appearance does not fit a lotion and the viscosity data do not demonstrate pseudoplastic behavior. L'Oreal stated the product flows with

minimum shear. FDA asked if the product is pourable. L'Oreal responded that it is pourable after taking a plastic rod and agitating for 30 seconds. FDA stated that pourability should not involve stirring and noted that when the container is turned upside down, the product does not flow. L'Oreal stated that their product flows with low stress and referred to the footnote. FDA reiterated that the product has not been shown to be pseudoplastic. L'Oreal disagreed with FDA's conclusion that their product is a cream and asked what additional data are necessary to demonstrate that their product is a lotion. FDA requested that L'Oreal provide rheology data for each of the formulations and L'Oreal agreed to provide it by January 25.

FDA asked if it is critical whether the product is a lotion or cream. L'Oreal stated that it is important from a marketing standpoint because consumers expect a lotion. This may set a precedent for future products.

FDA asked L'Oreal to provide samples in the dispensing bottles for all of their formulations to support their arguments. L'Oreal stated that this may be hard to do and they don't want to give us something that is not representative. L'Oreal asked if FDA would accept a lab batch in a container. FDA said if they submit a lab batch, we would need a rheogram along with the sample to show that it is representative. It was agreed that L'Oreal would send the samples by February 12, if available. L'Oreal will notify FDA of the availability of the samples by January 25.

2. FDA requested L'Oreal to provide batch analysis data for octocrylene used in the clinical/stability studies, including test results on impurities. The results provided to FDA in volume 1.3 page 107 did not include results on related substances for clinical batches.

L'Oreal agreed to obtain the original data on octocrylene for FDA and also to provide data on impurities in the drug substance.

3. FDA requested L'Oreal to provide retest results and batch numbers for avobenzone from Givaudan. L'Oreal asked what should be retested. FDA replied that the batch data in the DMF is very old for avobenzone. L'Oreal stated that another company owns the avobenzone material, but they will contact them about obtaining the data.
4. FDA has not received a response to the 1/17/06 and 1/19/06 requests, i.e., tightening the acceptance criteria for ecamsule, etc. L'Oreal is working on their response.

FDA asked about information requested on January 11. L'Oreal said everything is ready except one answer, but they can send what they have.

L'Oreal noted that there is an issue with NDA 21-471 in that the current supplier of titanium dioxide no longer wants to supply it. Along with a change in supplier, L'Oreal plans to change to a ~~_____~~ form of the drug. They asked what kind of evaluation work is appropriate. FDA suggested that they summarize the changes and submit their question when they submit the other data.

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/s/

Elaine Abraham
2/24/2006 02:03:34 PM
CSO

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(WO: 22, Mailstop 4447)

DATE RECEIVED: January 6, 2006
DATE OF DOCUMENT:
May 16, 2005

DESIRED COMPLETION DATE:
January 31, 2006
PDUFA DATE: March 16, 2006

ODS CONSULT #: 06-0010
06-0045

TO: Andrea Leonard Segal, M.D., Acting Director
Division of Nonprescription Clinical Evaluation, HFD-560

THROUGH: Nora Roselle, PharmD., Acting Team Leader
Denise Toyer, Pharm D., Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Linda M. Wisniewski, RN, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME:

Capital Soleil 15 (NDA 21-501)
(Avobenzone 2%, Ecamsule 3%, Octocrylene 10% Lotion)

Capital Soleil 20 (NDA 21-471)
(Avobenzone 2%, Ecamsule 3%, Octocrylene 10%, Titanium Dioxide 2% Lotion)

NDA SPONSOR:

L'Oreal USA Products

RECOMMENDATIONS:

Although the initial consult requested a review of the tradename, Capital Soleil, upon reviewing the labels and labeling we recognize the actual product names are Capital Soleil 15 and Capital Soleil 20. The numbers 15 and 20 represent the SPF rating which effectively differentiates these two product formulations. Thus, DMETS has no objections to the use of the proprietary names Capital Soleil 15 and Capital Soleil 20.

This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product. Additionally, all labeling comments in this review pertain to NDA's 21-501 and 21-502.
3. Because DDMAC does not have regulatory authority to review proposed OTC proprietary names, they did not comment on the name Capital Soleil.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-796-0538.

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
WO: 22; Mailstop: 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: January 18, 2006

NDA#: 21-501

NAME OF DRUG: Capital Soleil 15 (NDA 21-501)
(Avobenzone 2%, Ecamsule 3%, Octocrylene 10% Lotion)

Capital Soleil 20 (NDA 21-471)
(Avobenzone 2%, Ecamsule 3%, Octocrylene 10%, Titanium Dioxide 2% Lotion)

NDA HOLDER: L'Oreal USA Products

I. INTRODUCTION:

This consult was written in response to a request from the Division of Nonprescription Clinical Evaluation (HFD-560) for a review of the proprietary name, "Capital Soleil", regarding potential name confusion with other proprietary and/or established drug names. Capital Soleil is currently marketed by L'Oreal in Europe. Container labels, carton and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Capital Soleil is an over-the-counter (OTC) product that contains three ultraviolet radiation (UVR) filters providing protection throughout the ultraviolet B (UVB) and ultraviolet A (UVA) spectrum. These active ingredients include ecamsule, avobenzone, and octocrylene. Capital Soleil is indicated for the prevention of sunburn and is to be applied liberally 15 minutes before sun exposure. Reapply as needed or after towel drying, swimming or perspiring. A physician should be consulted for use in children under six months of age. Capital Soleil will be supplied in a tube containing 100 mL.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to Capital Soleil to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁴. The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was

¹ MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], Drugs@FDA, the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁵ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Capital Soleil. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. Because over-the-counter drug products are regulated by the FTC, DDMAC is unable to provide comments on the proposed trade name Capital Soleil.
2. The Expert Panel identified four proprietary names that were thought to have the potential for confusion with Capital Soleil. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel.

Product Name	Dosage form(s) Established name	Usual adult dose	Other
Capital Soleil TS Capital Soleil 20	Branamite/Azobenzene/Octocylene Lotion 2% 2% 10%	Apply liberally 15 minutes before sun exposure and reapply as needed.	NA
Capitol	Chloroxine Shampoo 2%	Massage thoroughly into wet scalp. Allow lather to remain on scalp for 3 minutes, rinse, and repeat. Two treatments per week.	LA/SA
Capoten	Captopril Tablets 12.5 mg, 25 mg, 50 mg, 100 mg	6.25 mg to 150 mg two to three times a day.	LA/SA
Capital with Codeine	Codeine Phosphate and Acetaminophen Suspension 12 mg/120 mg	15 mL every four hours.	LA/SA
Bain de Soleil	Mega Tan Sunscreen Lotion with Self Tanner SPF 4 Streakgarde Self Tanning Crème Dark Streakgarde Self Tanning Crème Deep Dark Radiance Eternelle Self Tanning Crème Medium Dark Radiance Eternelle Self Tanning Crème Dark Orange Gelee Sunscreen Lotion SPF 4 Special Set-Radiance Eternelle Self-Tanning Crème Dark Special Set-Radiance Eternelle Self-Tanning Crème Medium Dark	Apply as directed.	LA/SA

*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)

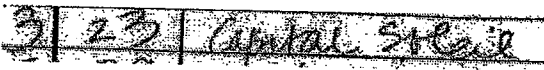
B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Capital Soleil were discussed by the Expert Panel.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Capital Soleil with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 125 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Capital Soleil (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Requisition #1: 	Order Code# 23 Capital Soleil 3 Bottles
Requisition #2: 	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See Appendix A for a complete listing of interpretations.

D. SAFETY EVALUATOR RISK ASSESSMENT

1. Look-alike and Sound-Alike Concerns

In reviewing the proprietary name Capital Soleil, the primary concerns related to look-alike and/or sound-alike confusion with Capitrol, Captopril, Capoten, Bain de Soleil, and Capital with Codeine.

Upon further review of the names gathered from EPD, the name Bain de Soleil was not reviewed further due to a lack of look-alike similarities with Capital Soleil as a result of the use of multiple modifiers within the Bain de Soleil product line (e.g. Mega Tan Sunscreen Lotion with Self Tanner SPF 4, Streakguarde Self Tanning Crème Dark, Streakguarde Self Tanning Crème Deep Dark, Radiance Eternelle Self Tanning Crème Medium Dark, Radiance Eternelle Self Tanning Crème Dark, Orange Gelee Sunscreen Lotion SPF 4, Special Set-Radiance Eternelle Self-Tanning Crème Dark, and Special Set-Radiance Eternelle Self-Tanning Crème Medium Dark).

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size.

- a. Capitrol was found to have look-alike and sound-alike potential with Capital Soleil if the 'Soleil' portion of the name is omitted or overlooked. Capitrol is a topical drug product and is indicated in the treatment of seborrheic dermatitis of the scalp. Both names contain six of the same letters in the same placement (C a p i t _ l vs. C a p i t _ _ l). This similarity in spelling contributes to an overall orthographic and phonetic similarity involving these two names. Both products are topically administered products that are supplied in one strength and one dosage form. This may result in either drug being ordered 'drug name use as directed', as this is not an unusual method of ordering topical products. However, Capital Soleil will be an over-the-counter product and is not likely to be stored on shelves with prescription items. This may help to prevent selection errors. DMETS believes that the different storage locations, in addition to the the entire name, Capital Soleil, will help to differentiate these two names when written.

Capital Soleil
Capitol

- b. Capoten may look or sound similar to Capital Soleil if the 'Soleil' portion of the name is omitted or overlooked. Capoten is indicated in the treatment of hypertension and heart failure. Both names contain the same four letters in the same placement (C a p _ t _ _). This spelling similarity may result in a similar phonetic pronunciation of each name. The upstroke for the last letter, 'l', in Capital in addition to the formal presentation of the name 'Capital Soleil', may help to differentiate these two products when written. There are differentiating product characteristics that may help to prevent error. They include dose (liberal amount vs. 6.25 mg to 150 mg), frequency of administration (before sun exposure or 'as needed' vs. two to three times daily), strength (3 %/2 %/10 % vs. 12.5

mg, 25 mg, 50 mg, and 100 mg), route of administration (topical vs. oral), and dosage form (lotion vs. tablet). Thus, the different doses, frequencies of administration, and strengths may help to differentiate these two products when ordered.

Capital Soleil

Capital

- c. Capital with Codeine may look and sound similar to Capital Soleil if the 'Soleil' or if the 'with Codeine' portion of the name is omitted or overlooked. Capital with Codeine is indicated in the treatment of pain. The first portion of each name is identical 'Capital', however, the formal name of each product includes additional portions that are orthographically and phonetically different (Soleil vs. with Codeine). Capital Soleil consists of two words with a total of 13 letters, whereas, Capital with Codeine consists of three words and a total of 18 letters thereby providing a lengthier orthographic appearance to the name. Additionally, the phonetic difference in the pronunciation of each name is noticeable. Although the first portion of each name is identical, the second portion of the name is phonetically different. Soleil is commonly pronounced similar to 'sew lay', whereas, Codeine is commonly pronounced similar to 'co' as in 'Coke' and 'deen'. Although both products are supplied in a single strength, which may be omitted in an order for either drug, there are some product characteristics that may help to differentiate each product when written or spoken. They include dose (liberal amount vs. 15 mL), frequency of administration (15 minutes before sun exposure vs. every four hours), route of administration (topical vs. oral), dosage form (lotion vs. oral suspension) and storage location (over-the-counter products vs. controlled prescription products). Moreover, since Capital Soleil will be an over-the-counter product, it is not likely to be stored near Capital with Codeine. Thus, the second portion of each name, (Codeine vs. Soleil), in addition to differentiating product characteristics, such as dose, frequency of administration, and storage location, will help to distinguish between these two products when ordered.

Capital Soleil

Capital with Codeine

- d. Captopril may look or sound similar to Capital Soleil if the 'Soleil' portion of the name is omitted or overlooked. Captopril is indicated in the treatment of hypertension and heart failure. Both names contain the same five letters in the same sequence but in different placements (C a p _ t _ l vs. C a p t _ _ _ l). This spelling similarity may result in a similar phonetic pronunciation of each name. Orthographically, both names are different. Where Capital contains one downstroke for the letter 'p', Captopril contains two downstrokes for the two 'p's, thereby providing a different orthographic appearance of each name. Moreover, the complete name of the product Capital Soleil includes a second portion of the name (Soleil) which will also help to differentiate these two products when written. There are differentiating product characteristics that may help to prevent error. They include dose (liberal amount vs. 6.25 mg to 150 mg), frequency of administration (before sun exposure or 'as needed' vs. two to three times daily), strength (3 %/2 %/10 % vs. 12.5 mg, 25 mg, 50 mg, and 100 mg), route of administration (topical vs. oral), and dosage form (lotion vs. tablet). Thus, the orthographic differences, in addition to the

different doses, frequencies of administration, and strengths may help to differentiate these two products when ordered.

Capital Soleil
Capitol

2. Differentiation of Capital Soleil products that Contain Different Active Ingredients

We note that the sponsor proposes to market two products containing two different sets of active ingredients (avobenzone, ecamsule, octocrylene vs. avobenzone, ecamsule, octocrylene, titanium dioxide) with the same proprietary name, Capital Soleil. This is concerning because consumers would not know by the name alone that there are different active ingredients in each. If a consumer is allergic to a specific ingredient they may not realize that the active ingredients of Capital Soleil may be different depending upon the SPF they choose. However, DMETS recognizes that the current practice, of naming OTC sunscreens, is to use the same proprietary name and distinguish them by using descriptors and/or the SPF number. Although DMETS does not recommend the use of the same proprietary name for products that contain different active ingredients for prescription products, we acknowledge that there is precedent for this naming convention with sunscreens in the Division of Nonprescription Clinical Evaluation. We also note that the sponsor prominently displays the SPF rating on the Principal Display Panel of each label thereby adequately differentiating each formulation.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

We note that the sponsor has several pending proprietary name reviews with DMETS that may include similar labels and labeling. Therefore, we will provide General Comments, in this review, that are applicable to all of the proprietary names and address any specific comments pertinent to each proprietary name in the respective reviews.

In the review of the container labels, carton and insert labeling of Capital Soleil, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENT (All products)

1. Sun Protection Factor (SPF) is a recognized abbreviation on U.S. marketed sunscreens. However, the sponsor also uses — o indicate — DMETS questions whether this is a recognized term currently used and whether patients are aware of its meaning. If — is not recognized by users, then DMETS recommends deleting this term from the labels and labeling. If — s allowed, then the sponsor should use an asterisk (*) on the principal display panel to refer user to the back panel where — is defined.
2. Delete references to — , since this statement appears promotional and does not communicate additional information to healthcare practitioners or patients.

3. DMETS notes that the term '*MexorylTM SX*' is a trademark for Ecamsule and the term '*Parsol®*' is a trademark for Avobenzone. Since the active ingredients, Ecamsule and Avobenzone, must be listed as part of the established name and active ingredients, delete all references to '*MexorylTM SX* and *Parsol®*, as they may be a source of confusion to patients who may think that this is a fourth or fifth active ingredient in the product.
4. Eliminate terminal zeros in the expression of strength and volume throughout labels and labeling. DMETS notes several incidents where a terminal zero is used in expression of the strength. The use of terminal zeros may result in error as often the decimals are overlooked. As evidenced by our post-marketing surveillance, the use of terminal zeros could potentially result in a ten-fold medication dose error. Although it is unlikely that a ten-fold dosing error would occur in this instance, the use of terminal zeros in the expression of strength or volume is not in accordance with the General Notice (page 10) of the 2004 USP, which states, '...to help minimize the possibility of error in the dispensing of administration of drugs...the quantity of active ingredients when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero.' In addition, the use of terminal zeros is specially listed as a dangerous abbreviation, acronym, or symbol in the 2006 National patient Safety Goals of the Joint Commission of Accreditation of Healthcare Organizations (JCAHO). Lastly, safety groups such as ISMP also list terminal zeros on their dangerous abbreviations and dose designations list.
5. The proposed container label and carton labels were provided in black and white, and may not represent the true color of the labels. Therefore, DMETS cannot assess if there are any safety concerns due to the colors utilized on the labels.

B. CONTAINER LABEL (Main Display Panel)

Include a statement of identity on the primary display panel to be in accordance with 21 CFR 201.61. 'The principal display panel of an over-the-counter drug in package form shall bear as one of its principal features a statement of the identity of the commodity. Such statement of identity shall be in terms of the established name of the drug, if any there be, followed by an accurate statement of the general pharmacological category (ies) of the drug or the principal intended action (s) of the drug....The statement of identity shall be presented in bold face type on the principal display panel, shall be in a size reasonably related to the most prominent printed matter on such panel, and shall be in lines generally parallel to the base on which the package rests as it is designed to be displayed....'

Appendix A:

ODS Consult: 06-0010 Capital Soleil

Voice	Inpatient Written	Outpatient Written
Cap Sole	Capital Solere	Capital Soleil
Capital Solay	Capiral Soleve	Capiral Soleil
Capital Solé	Capital Soeve	Capital Solei
Capital Solei	Capital Soleil	Capital Soleil
Capital Soleil	Capital Soleil	Capital Soleil
Capital Soleil	Capital Soleil	Capital Soleil
Capital Soley	Capital Solere	Capital Soleil
Capitol Solay	Capital Solere	Capital Soleil
Capitol Sole	Capital Solere	capital soleil
Capitol Solle	Capital Solere	Capital Soleil
Solay	Capital Solere	Capital Soleil
Solay	Capital Solerl	Capital Soleil
Soleil	Capital Solerl	Capital Soleil
	Capital Soleve	Capital Soleil
	Capital Sollex	Capital Soleil
	Capital solution	Capital Soleil
	Capitol Soleil	Capital Soleil
	Capitol Solert	Capital Solene
	Capitol Solert	Capital Solution

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

/s/

Linda Wisniewski
2/14/2006 11:35:02 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
2/14/2006 11:57:25 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
2/14/2006 12:16:49 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

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

DATE: January 31, 2006

FROM: Susan McCune, MD
Division of Pediatric Drug Development, OCTAP

Dianne L. Kennedy, MPH, RPH
Pregnancy & Lactation Team, OND

THROUGH: Sandra Kweder, MD
Deputy Director, OND

TO: Elaine Abraham, RPM
DNCE

SUBJECT: Combination OTC Sunscreens (Investigational Name –
and Use During Pregnancy
NDAs: 21-501, 21-502, & 21-471 (L'Oreal USA Products))

Consult received by the PLT: December 8, 2005
Due date: January 31, 2006

I. EXECUTIVE SUMMARY

L'Oreal USA Products is seeking approval to market three new sunscreen products with three or four sunscreen ingredients in differing concentrations. These ingredients are avobenzene, octocrylene, titanium dioxide (all three monograph ingredients) and ecamsule (a new ingredient). Eleven women became pregnant during three studies, four infants developed birthmarks: two with hemangiomas, one with a nevus flammeus and one with a café au lait spot.

The Pregnancy & Lactation Team (PLT) was consulted to

1. Provide feedback on whether or not the sponsor should conduct studies to evaluate children of mothers exposed to the new sunscreen formulations during pregnancy for cutaneous vascular abnormalities.
2. Advise whether the OTC labeling for these new sunscreen products should carry any pregnancy warnings.

The PLT recommends that the sponsor be requested to provide more descriptive information on the seriousness and extent of vascular involvement for the two

cases of hemangiomas as well as the dose and duration of exposure to the drug. Given that hemangiomas develop postnatally frequently (7 – 10% of infants) and most are small and involute, the PLT does not recommend setting up a pregnancy exposure registry unless there is something unusual about the two cases, e.g., very large, life-threatening, deep, etc.

The PLT does not recommend requiring a pregnancy warning on the OTC labeling for these products for the following reasons:

- Ecamsule is a Pregnancy Category B drug according to the Pharm/Tox review.
- PK studies show that <1% of ecamsule is absorbed systemically
- There is no evidence of reproductive toxicity for titanium oxide, ecamsule, avobenzone or octocrylene in the literature although the data are sparse.
- There are no reports in the literature or in AERS of hemangiomas associated with the use of titanium oxide, ecamsule, avobenzone or octocrylene.

II. BACKGROUND

The following was information provided in the written consult request:

“The sponsor is requesting approval to market three new sunscreen drug products _____ in the over-the-counter setting (NDAs 21-501, 21-502, and 21-471). All three sunscreens contain three or four active sunscreen ingredients in different concentrations: avobenzone, octocrylene, titanium dioxide (all three monograph ingredients) and ecamsule (a new ingredient). In addition, _____

Altogether, 11 women became pregnant during studies with _____ formulas or similar formulations. One woman (Subject #60 in Study 1.CG.03.SRE.2604) discontinued due to pregnancy and withdrew from treatment and the study. The remaining 10 women became pregnant during 2 or 4 long-term safety studies (PEN.750.02 and RD.06.SRE.18047). There were no pregnancies reported during any other studies.

Four women became pregnant in Study PEN.750.02. Two of these subjects (#12-18 and #16-35) delivered during the study. Subject 11-16 discontinued the study prior to giving birth and subject 12-36 gave birth after completing the study. All four women delivered normal healthy babies.

Six pregnancies were reported during Study RD.06.SRE.18047. Of the six women who reported pregnancy, three discontinued because of their pregnancy. Two of the six pregnancies resulted in a delivery of normal healthy babies. One infant developed a café au lait spot 1 to 2 weeks after birth. Since isolated café au lait spots occur in up to 10-20% of the normal population, the event was assessed

by the sponsor as of no pathological significance. Three of six infants were normal at birth but subsequently developed vascular lesions approximately three months after birth. All three events of birthmarks (two hemangiomas and one nevus flammeus) were reported as serious adverse events (congenital anomaly). Family history was negative in two cases and positive in one (nevus flammeus). For the two cases of hemangioma, the events were considered possibly related to study treatment; the case of nevus flammeus was considered of unlikely relationship to study treatment.

According to the pharmacology review, ecamsule is a Pregnancy Category B drug. Based on the preclinical data, ecamsule is not a teratogen and does not have an effect on reproductive function in animals. The division does not have data for the other two monograph active ingredients (avobenzone and octocrylene), which are not contraindicated in pregnancy. The number of women exposed to the sunscreen formulations containing ecamsule is small. Three congenital vascular adverse events occurred in subjects with PLME could have occurred by chance alone. Nevertheless, the exposure to drug product could be significant if used as directed. PK studies show that <1% of ecamsule (active ingredient) is absorbed systemically."

III. REVIEW OF DATA

The following materials were reviewed:

- Medical Officer review of _____
- Pharm/Tox review of _____
- Reprotox information in the online Micromedex Integrated Index including Teris – The Teratogen Information System, the Reprotox System and Shepard's Catalog of Teratogenic Agents
- AERs database
- Pubmed for 1. reproductive effects with avobenzone, octocrylene, titanium dioxide or ecamsule and 2. hemangiomas. The following articles were retrieved.
 - Blei F. Basic science and clinical aspects of vascular anomalies. *Current Opinion in Pediatrics* 2005;17:5011-9.
 - Chiller KG, Frieden IJ, Arbiser JL. Molecular pathogenesis of vascular anomalies: Classification into three categories based upon clinical and biochemical characteristics. *Lymphatic Research and Biology* 2003;1(4):267-81.
 - Chang MW. Updated classification of hemangiomas and other vascular anomalies. *Lymphatic Research and Biology* 2003;1(4):259-65.

The medical officer review and the pharm/tox review are from the previous submission _____ There is no information from the current submission other than what is included in the written consult. It appears that 3 studies contained women who became pregnant (N=11). One woman in study 1.CG.03.SRE.2604 became pregnant and

discontinued her participation in the trial. Four women in study PEN.750.02 became pregnant and all delivered healthy babies. Six pregnancies were reported in study RD.06.SRE.18047 which was reviewed for _____. Of the 6 pregnancies, 3 infants developed "vascular lesions" approximately 3 months after birth. One was a nevus flammeus and two were reported as hemangiomas. There was no description of the hemangiomas. Dr. _____ stated that nevus flammeus is present in half of all newborns and hemangiomas occur in 10-13% of children in the first year of life. He was unaware of any reports that hemangiomas have been induced by exogenous factors such as drugs or chemicals. He felt that the hemangiomas were random findings and not related to the use of the sunscreen.

The consult mentions another patient with a cafe au lait spot but that is not discussed in the medical officer review of _____. According to the consult, the cafe au lait spot was felt to be of no pathological significance "since isolated cafe au lait spots occur in up to 10-20% of the normal population".

In the Pharm/Tox review of _____ there was an oncogenicity study by dermal application of ecamsule to CD-1 mice for 104 weeks (p.45-51). They concluded, "The relative incidence of hemangiosarcomas compared to controls was higher in the high dose males and females. The relative incidence of hemangiomas in treated females was also increased over control. However, hemangiomas and hemangiosarcomas are not rare in the historical control data from the testing laboratory and the values from the current study appear to be within historical control ranges."

There is no evidence of reproductive toxicology for titanium dioxide, ecamsule, avobenzone or octocrylene in the literature although the data are sparse.

There are no reports in the literature of hemangiomas associated with ecamsule, avobenzone, octocrylene or titanium dioxide.

In a search of the AERS database for ecamsule, avobenzone, octocrylene, titanium oxide, and penipiro, there were a total of 61 reports. None of them mentioned hemangioma. There were no AERS reports for any children between 0-1 year of age, and there were no reports of congenital anomalies.

The literature supports the assessment that nevus flammeus occurs in approximately half of all newborns, cafe au lait spots in approximately 10 % of infants and hemangiomas in approximately 7-10% of the newborn population. Hemangiomas are more common in female infants and premature infants. They tend to grow postnatally for several months and then spontaneously involute. There are many varieties of hemangiomas in the newborn period and there was no description of the type of hemangioma in the study report. The etiology of vascular anomalies in the newborn period is unclear and likely represents a multifactorial process.

IV. CONCLUSIONS

Cutaneous vascular abnormalities occur frequently in the newborns. Unless the two cases of hemangiomas reported in the study are unusual for some reason, e.g., very large, life-threatening, deep, etc. the PLT does not see a need for a pregnancy exposure registry.

Based on the materials reviewed the PLT does not recommend a pregnancy warning be included in the OTC labeling.

Susan McCune, MD
Division of Pediatric Drug Development,
OCTAP

Dianne L. Kennedy, MPH, RPh
Pregnancy & Lactation Team,
OND

Cc: OND: Kweder, Kennedy
DPPD: Mathis, McCune
DNCE: Leonard Segal, Abraham

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this page is the manifestation of the electronic signature.

/s/

Matthew Bacho

2/1/2006 01:55:32 PM

CSO

PLT Consult for NDAs 21-471, 21-501, and 21-502

Sandra L. Kweder

2/8/2006 05:42:15 PM

MEDICAL OFFICER

MEMORANDUM

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

DATE: January 31, 2006

FROM: Susan McCune, MD
Division of Pediatric Drug Development, OCTAP

Dianne L. Kennedy, MPH, RPH
Pregnancy & Lactation Team, OND

THROUGH: Sandra Kweder, MD
Deputy Director, OND

TO: Elaine Abraham, RPM
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The Pregnancy & Lactation Team (PLT) was consulted to

1. Provide feedback on whether or not the sponsor should conduct studies to evaluate children of mothers exposed to the new sunscreen formulations during pregnancy for cutaneous vascular abnormalities.
2. Advise whether the OTC labeling for these new sunscreen products should carry any pregnancy warnings.

The PLT recommends that the sponsor be requested to provide more descriptive information on the seriousness and extent of vascular involvement for the two

cases of hemangiomas as well as the dose and duration of exposure to the drug. Given that hemangiomas develop postnatally frequently (7 – 10% of infants) and most are small and involute, the PLT does not recommend setting up a pregnancy exposure registry unless there is something unusual about the two cases, e.g., very large, life-threatening, deep, etc.

The PLT does not recommend requiring a pregnancy warning on the OTC labeling for these products for the following reasons:

- Ecamsule is a Pregnancy Category B drug according to the Pharm/Tox review.
- PK studies show that <1% of ecamsule is absorbed systemically
- There is no evidence of reproductive toxicity for titanium oxide, ecamsule, avobenzone or octocrylene in the literature although the data are sparse.
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II. BACKGROUND

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Six pregnancies were reported during Study RD.06.SRE.18047. Of the six women who reported pregnancy, three discontinued because of their pregnancy. Two of the six pregnancies resulted in a delivery of normal healthy babies. One infant developed a café au lait spot 1 to 2 weeks after birth. Since isolated café au lait spots occur in up to 10-20% of the normal population, the event was assessed

by the sponsor as of no pathological significance. Three of six infants were normal at birth but subsequently developed vascular lesions approximately three months after birth. All three events of birthmarks (two hemangiomas and one nevus flammeus) were reported as serious adverse events (congenital anomaly). Family history was negative in two cases and positive in one (nevus flammeus). For the two cases of hemangioma, the events were considered possibly related to study treatment; the case of nevus flammeus was considered of unlikely relationship to study treatment.

According to the pharmacology review, ecamsule is a Pregnancy Category B drug. Based on the preclinical data, ecamsule is not a teratogen and does not have an effect on reproductive function in animals. The division does not have data for the other two monograph active ingredients (avobenzone and octocrylene), which are not contraindicated in pregnancy. The number of women exposed to the sunscreen formulations containing ecamsule is small. Three congenital vascular adverse events occurred in subjects with PLME could have occurred by chance alone. Nevertheless, the exposure to drug product could be significant if used as directed. PK studies show that <1% of ecamsule (active ingredient) is absorbed systemically."

III. REVIEW OF DATA

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- Pubmed for 1. reproductive effects with avobenzone, octocrylene, titanium dioxide or ecamsule and 2. hemangiomas. The following articles were retrieved.
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 - Chang MW. Updated classification of hemangiomas and other vascular anomalies. *Lymphatic Research and Biology* 2003;1(4)259-65.

The medical officer review and the pharm/tox review are from the previous submission _____). There is no information from the current submission other than what is included in the written consult. It appears that 3 studies contained women who became pregnant (N=11). One woman in study 1.CG.03.SRE.2604 became pregnant and

discontinued her participation in the trial. Four women in study PEN.750.02 became pregnant and all delivered healthy babies. Six pregnancies were reported in study RD.06.SRE.18047 which was reviewed for ~~_____~~. Of the 6 pregnancies, 3 infants developed "vascular lesions" approximately 3 months after birth. One was a nevus flammeus and two were reported as hemangiomas. There was no description of the hemangiomas. Dr. ~~_____~~ stated that nevus flammeus is present in half of all newborns and hemangiomas occur in 10-13% of children in the first year of life. He was unaware of any reports that hemangiomas have been induced by exogenous factors such as drugs or chemicals. He felt that the hemangiomas were random findings and not related to the use of the sunscreen.

The consult mentions another patient with a cafe au lait spot but that is not discussed in the medical officer review of ~~_____~~. According to the consult, the cafe au lait spot was felt to be of no pathological significance "since isolated cafe au lait spots occur in up to 10-20% of the normal population".

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In a search of the AERS database for ecamsule, avobenzene, octocrylene, titanium oxide, and penipr, there were a total of 61 reports. None of them mentioned hemangioma. There were no AERS reports for any children between 0-1 year of age, and there were no reports of congenital anomalies.

The literature supports the assessment that nevus flammeus occurs in approximately half of all newborns, cafe au lait spots in approximately 10 % of infants and hemangiomas in approximately 7-10% of the newborn population. Hemangiomas are more common in female infants and premature infants. They tend to grow postnatally for several months and then spontaneously involute. There are many varieties of hemangiomas in the newborn period and there was no description of the type of hemangioma in the study report. The etiology of vascular anomalies in the newborn period is unclear and likely represents a multifactorial process.

IV. CONCLUSIONS

Cutaneous vascular abnormalities occur frequently in the newborns. Unless the two cases of hemangiomas reported in the study are unusual for some reason, e.g., very large, life-threatening, deep, etc. the PLT does not see a need for a pregnancy exposure registry.

Based on the materials reviewed the PLT does not recommend a pregnancy warning be included in the OTC labeling.

Susan McCune, MD
Division of Pediatric Drug Development,
OCTAP

Dianne L. Kennedy, MPH, RPh
Pregnancy & Lactation Team,
OND

Cc: OND: Kweder, Kennedy
DPPD: Mathis, McCune
DNCE: Leonard Segal, Abraham

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

/s/

Matthew Bacho

2/1/2006 01:55:32 PM

CSO

PLT Consult for NDAs 21-471, 21-501, and 21-502

Sandra L. Kweder

2/8/2006 05:42:15 PM

MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-471

L'Oreal USA Products, Inc.
Attention: Jean R. Grieve
Assistant Vice President, Drug Approval Group
30 L'Oreal Way
Clark, NJ 07066

Dear Ms. Grieve:

Please refer to your September 27, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for 2% ecamsule/2% avobenzone/10% octocrylene/2% titanium dioxide lotion.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on November 27, 2005 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Elaine Abraham, Regulatory Project Manager, at (301) 796-0843.

Sincerely,

{See appended electronic signature page}

Leah Christl, Ph.D.
Acting Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

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/s/

Leah Christl

12/8/2005 07:45:02 AM



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products
Division of Nonprescription Clinical Evaluation

FACSIMILE TRANSMITTAL SHEET

DATE: November 4, 2005

To: Jean Grieve	From: Elaine Abraham Project Manager
Company: L'Oreal USA Products	Division of Nonprescription Clinical Evaluation Office of Nonprescription Products
Fax number: (732) 909-2007	Fax number: (301) 796-9899
Phone number: (732) 680-5562	Phone number: (301) 796-0843
Subject: NDA 21-501, 21-502, 21-471 information request	

Total no. of pages including cover: 2

Comments:

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2060. Thank you.

We reference your original NDAs 21-501, 21-502, and 21-471 and have the following request for information:

The acceptance criteria for related substances in Table 4.A. 3-12 (drug product specification) appeared to exceed the ICH Q3B qualification thresholds. The safety of these related substances in the drug product should be addressed. This may be addressed with information demonstrating that these related substances were tested in clinical studies, nonclinical data, or data from human exposure to these related substances from other products.

Please provide:

- (1) the toxicology data available for these related substances and/or similar compounds
- (2) information on the levels of these impurities on the batches tested in clinical studies, and/or
- (3) information regarding these related substances in any marketed products including the specifications and human use data.

If any batch of the drug product which contained these related substances has been tested in the Pharmacology/Toxicology studies shown in Item 5, Table 5.1, please provide the results of batch data analysis or Certificates of Analysis, including the amounts of these related substances.

The acceptance criterion for "individual unknown" should be below the ICH Q3B qualification threshold (0.15% for maximum daily dose of >2g).

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ON ORIGINAL

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/s/

Elaine Abraham

11/4/2005 02:31:54 PM

CSO

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-471	Efficacy Supplement Type SE-	Supplement Number
Drug: 2% ecamsule/2% avobenzone/10% octocrylene/2 % titanium dioxide cream		Applicant: L'Oreal USA Products, Inc.
RPM: Elaine Abraham	HFD-560	Phone # (301) 796-0843
Application Type: () 505(b)(1) (X) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct. (X) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Avobenzone (sunscreen monograph) Octocrylene (sunscreen monograph) Titanium dioxide (sunscreen monograph)	
❖ Application Classifications:		
Review priority	(X) Standard () Priority	
Chem class (NDAs only)	4	
Other (e.g., orphan, OTC)	OTC	
❖ User Fee Goal Dates		
		October 9, 2006
❖ Special programs (indicate all that apply)		
		(X) None Subpart H () 21 CFR 314.510 (accelerated approval) () 21 CFR 314.520 (restricted distribution) () Fast Track () Rolling Review () CMA Pilot 1 () CMA Pilot 2
User Fee Information		
User Fee	(X) Paid UF ID number 4263	
User Fee waiver	() Small business () Public health () Barrier-to-Innovation () Other (specify)	
User Fee exception	() Orphan designation () No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) () Other (specify)	
❖ Application Integrity Policy (AIP)		

Applicant is on the AIP	☐ Yes ☒ No
This application is on the AIP	☐ Yes ☒ No
Exception for review (Center Director's memo)	
OC clearance for approval	
Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	☒ Verified
❖ Patent	
Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified
Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) ☐ Verified <i>N/A-No patents in OB</i> 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).</i>	☒ N/A (no paragraph IV certification) ☐ Verified
[505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.	
Answer the following questions for each paragraph IV certification:	
Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?	☐ Yes ☐ No
(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).	
If "Yes," skip to question (4) below. If "No," continue with question (2).	
Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?	☐ Yes ☐ No
If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).	
If "No," continue with question (3).	
Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)

Exclusivity summary

Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)

No

Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.

☐ Yes, Application # _____
☒ No

Administrative Reviews (Project Manager, ADRA) (indicate date of each review)

6/21/05, 2/24/06, 9/21/06

General Information

Actions	
Proposed action	(X) AP () TA () AE () NA
Previous actions (specify type and date for each action taken)	AE 7/26/06
Status of advertising (approvals only)	() Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
Press Office notified of action (approval only)	() Yes (X) Not applicable
Indicate what types (if any) of information dissemination are anticipated	(X) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
Division's proposed labeling (only if generated after latest applicant submission of labeling)	
Most recent applicant-proposed labeling	8/8/06, 9/22/06
Original applicant-proposed labeling	9/27/05
Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>)	7/21/06, 10/4/06
Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
Division proposed (only if generated after latest applicant submission)	
Applicant proposed	
Reviews	
Post-marketing commitments	
Agency request for post-marketing commitments	PREA commitment
Documentation of discussions and/or agreements relating to post-marketing commitments	
Outgoing correspondence (i.e., letters, E-mails, faxes)	12/8/05, 11/4/05, 3/10/06, 3/17/06, 5/23/06, 7/18/06, 9/11/06, 9/14/06
Memoranda and Telecons	1/23/06, 2/10/06, 7/24/06, 10/12/06
Minutes of Meetings	
EOP2 meeting (indicate date)	1/24/01
Pre-NDA meeting (indicate date)	9/18/01
Pre-Approval Safety Conference (indicate date; approvals only)	
Other	
Advisory Committee Meeting	
Date of Meeting	N/A
48-hour alert	
Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	5/21/99 (64 FR 27666)

Summary Application Review

Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	3/6/06, 7/25/06
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	1/9/06, 3/7/06, 5/14/06
❖ Microbiology (efficacy) review(s) (indicate date for each review)	
Safety Update review(s) (indicate date or location if incorporated in another review)	1/30/06 in clin review
Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	
Pediatric Page (separate page for each indication addressing status of all age groups)	9/21/06
Demographic Worksheet (NME approvals only)	
❖ Statistical review(s) (indicate date for each review)	N/A
❖ Biopharmaceutical review(s) (indicate date for each review)	2/21/06
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	
❖ Clinical Inspection Review Summary (DSI)	
Clinical studies	4/27/06
Bioequivalence studies	
CMC Information	
❖ CMC review(s) (indicate date for each review)	6/30/06, 9/14/06
Environmental Assessment	
Categorical Exclusion (indicate review date)	6/30/06
Review & FONSI (indicate date of review)	
Review & Environmental Impact Statement (indicate date of each review)	
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	11/30/05
❖ Facilities inspection (provide EER report)	Date completed: 3/29/06 (X) Acceptable () Withhold recommendation
Methods validation	() Completed N/A () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	2/2/06
Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	

ITEM 18

NDA 21-471

USER Fee # 4263

SPF 20 Water Resistant Sunscreen Lotion

Attached please find three User Fee Cover Sheets and corresponding copies of checks sent to:

U.S. Food and Drug Administration
Mellon Client Service Center RM 670
500 Ross Street
Pittsburgh, PA 15262-0001

The cumulative total of these checks yields the User Fee amount of \$672,000.00, the fee rate for fiscal year 2005 for New Drug Application requiring clinical data.

1 st Check	December 20, 2001	\$ 309,647.00
2 nd Check	December 18, 2003 (equal to Fiscal 2004 User Fee)	\$ 263,853.00
3 rd Check	December 7, 2004 (increase in User Fee for Fiscal 2005)	<u>\$ 98,500.00</u>
	Total Paid	
	Fiscal 2005 User Fee	\$ 672,000.00

**APPEARS THIS WAY
ON ORIGINAL**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

L'ORÉAL SA
L'ORÉAL USA Products Inc.
(Official agent for L'ORÉAL SA)
111 Terminal Avenue
CLARK, NJ 07066

3. PRODUCT NAME

MEXORYL[®] SX 20 (ecamsule)

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE
AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY
REFERENCE TO

(APPLICATION NO. CONTAINING THE DATA).

Note: NDA User Fee Payment in advance of
NDA submission

2. TELEPHONE NUMBER (Include Area Code)

(732) 499-6600

5. USER FEE I.D. NUMBER

4263

6. LICENSE NUMBER / NDA NUMBER

N021471

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT
APPROVED UNDER SECTION 505 OF THE FEDERAL
FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN
EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,
Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT
QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of
the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL
GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED
COMMERCIALY
(Self Explanatory)

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR
TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT
FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT
LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL
APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not
required to respond to, a collection of information unless it
displays a currently valid OMB control number.

Please DO NOT RETURN this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

Cheryl M. Sanzane

TITLE

AVP Scientific & Drug
Regulatory Affairs

DATE

December 19, 2001

FORM FDA 3397 (6/98)

Created by Electronic Document Services/USDHHS: (301) 443-2454 EP

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

See Instructions on Reverse Side Before Completing This Form

Completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS L'ORÉAL SA L'ORÉAL USA Products Inc. (Official agent for L'ORÉAL SA) 30 Terminal Ave. CLARK, NJ 07066	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER NO21471
2. TELEPHONE NUMBER (Include Area Code) (732) 680-5562	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? ☐ YES ☐ NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: ☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. ☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: Note: Partial payment previously made (APPLICATION NO. CONTAINING THE DATA)
3. PRODUCT NAME MEXORYL[®] SX 20, WR (ecamsule)	6. USER FEE I.D. NUMBER 4263

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

- | | |
|--|---|
| ☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) | ☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.) |
| ☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.) | ☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory) |

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

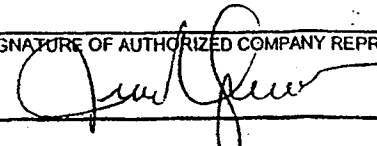
(See item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and
Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Assistant Vice President Drug Approval Group	DATE 12/19/03
---	--	-----------------------------

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: December 31, 2006.

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS L'ORÉAL SA L'ORÉAL USA Products Inc. (Official agent for L'ORÉAL SA) 30 Terminal Ave Clark, NJ 07066	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER N021471
2. TELEPHONE NUMBER (Include Area Code) (732) 680-5562	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? ☐ YES ☐ NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: ☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. ☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: <u>PRE/Advance Submission Payment</u> <u>Note: Partial payments previously made</u> (APPLICATION NO. CONTAINING THE DATA).
3. PRODUCT NAME Mexoryl® SX 20, WR (ecamsule)	6. USER FEE I.D. NUMBER 4263

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

- | | |
|--|---|
| ☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) | ☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See Item 7, reverse side before checking box.) |
| ☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See Item 7, reverse side before checking box.) | ☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory) |

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

TITLE

Assistant Vice President
Drug Approval Group

DATE

12-10-04