CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-501

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA Number (s)	21-501, 21-502 and 21-471
Submission Date(s)	16th May, 2005; 12th May, 2005 and September 27th, 2005
Brand Name(s)	(b) (4) SPF 15 Water Resistant (W/R) Sunscreen Lotion , (b) (4) SPF 15 Sunscreen Daily Lotion, (b) (4) SPF 20 Water Resistant (W/R) Sunscreen Lotion (***Brand Names are currently being Reviewed by DMETS***)
Generic Name	Ecamsule 3%, Avobenzone 2%, and Octocrylene 10%, Ecamsule 2%, Avobenzone 2%, and Octocrylene 10%, Ecamsule 2%, Avobenzone 2%, Octocrylene 10%, and Titanium Dioxide 2 %
Reviewer	Abimbola Adebowale Ph.D.
Team Leader	Dennis Bashaw Pharm D.
OCPB Division	DCP3
OND Division	OND-540
Sponsor	L'Oreal USA Products, Inc. Clark NJ 07066
Relevant IND(s)	59,126
Submission Type; Code	Original NDAs for OTC use ; 4S
Formulation; Strength(s)	Lotions
Indication	To prevent sunburn (b) (4) due to sun exposure

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1 Executive Summary

L'Oreal has developed three new combination sunscreen drug products namely, (b) (4) SPF 15 Water Resistant (W/R) Sunscreen Lotion, (b) (4) SPF 15 Sunscreen Daily Lotion and, (b) (4) SPF 20 Water Resistant (W/R) Sunscreen Lotion, for over-the-counter (OTC) use in adults and children 6 months of age and older.

Two of the products (b) (4) SPF 15 W/R Sunscreen Lotion and (b) (4) SPF 15 Sunscreen Daily Lotion, contain three active ingredients (ecamsule, avobenzone and octocrylene) in different concentrations. (b) (4) SPF 20 Water Resistant (W/R) Sunscreen Lotion contains the same three active ingredients at the same concentrations as (b) (4) SPF 15 Sunscreen Daily Lotion, plus an additional ingredient (titanium dioxide). Avobenzone, octocrylene and titanium dioxide are currently marketed OTC under the Tentative Final Monograph for Sunscreen Products for Human Use. In the proposed (b) (4) Sunscreen Lotions, avobenzone, octocrylene and titanium dioxide are being used within the specified amounts and indications of the OTC monograph.

Ecamsule is a new chemical entity. Ecamsule was previously studied under

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, the (b) (4) Sunscreen lotions are intended for children aged 6 months and older.

In this submission, the applicant has provided the previously submitted in vivo data for cream combined with the in vitro-permeation study previously submitted to evaluate the impact of reformulation ((e.g. triad products (i.e. (b) (4) SPF 15 W/R Sunscreen Lotion and (b) (4) SPF 15 Sunscreen Daily Lotion,) against the cream)) on the bioavailability of ecamsule. This approach to fulfill the Agency's BA requirements was found acceptable by OCPB at the End-of-Phase 2 meeting held on January 24th, 2001 (meeting minutes in DFS dated 4/4/01). Since the clinical pharmacology and biopharmaceutics data provided to support the marketing of all three (b) (4) Sunscreen Lotions are the same, the three NDAs are being reviewed together.

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1.1 Recommendation (s):

The totality of the clinical pharmacology data for ecamsule, the non-clinical toxicity data, the in vitro data and, the safety data obtained from the clinical studies and post marketing studies all combined together indicate that the systemic exposure of ecamsule following the topical application of (b) (4) SPF 15 W/R Sunscreen Lotion, (b) (4) SPF 15 Sunscreen Daily Lotion and, (b) (4) SPF 20 W/R Sunscreen Lotion is minimal. The data also indicates that the effect of ecamsule on the systemic exposure of the combination of the three other active ingredients (octocrylene, avobenzone and titanium dioxide) is minimal and unlikely to be clinically relevant from a safety perspective.

Following concurrence with the medical reviewer (Dr. D. Shetty), the clinical pharmacology information to support pediatric systemic exposure combined with, the safety data obtained from the clinical studies and post-marketing data is adequate to support the proposed labeling of the three (b) (4) Sunscreen Lotions for use in children down to six months of age.

Based on the data submitted, the applicant has met the requirements outlined in 21CFR 320 and, their application is acceptable from a clinical pharmacology perspective.

Labeling Recommendation (to be conveyed to the applicant):

Based on the documented interactions in the literature between sunscreens and, estradiol topical emulsion (i.e. Estrasorb) and DEET, the following label is recommended:

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1.2 Phase IV Commitments: None were identified.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics (CPB) Findings

The applicant did not conduct any clinical pharmacology studies with the (b) (4) SPF 15 W/R Sunscreen Lotion (NDA 21-501), (b) (4) SPF 15 Sunscreen Daily Lotion (NDA 21-502), or (b) (4) SPF 20 W/R Sunscreen Lotion (NDA 21-471). However, the applicant provided the clinical pharmacology data that was obtained for a related drug product . The clinical pharmacology studies for cream mainly investigated the systemic exposure of ecamsule (the new chemical entity) after topical administration of formulations consisting of concentrations ranging from 2 - 4.95%.

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Although cream consists of the active ingredients (ecamsule) in the three (b) (4) lotions, there are variations between the (b) (4) lotions and cream in terms of what active ingredients are present and their concentrations (see table below).

IND product name	SPF 20 W/R[1]	SPF 15 Daily	SPF 15 W/R	
IND number	59,126	59,126	59,126	
NDA application no.	21-471	21-502[2]	21-501[3]	
Ingredients:				
Ecamsule	2%	2%	3%	3%
Avobenzone	2%	2%	2%	
Octocrylene	10%	10%	10%	
Titanium dioxide	2%	--	--	

[1] The proposed drug product of this application
[2] NDA submitted on May 12, 2005
[3] NDA submitted on May 16, 2005

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In this submission, the applicant has provided the previously submitted in vivo data for ——— Cream combined with the in vitro-permeation study that was previously submitted to evaluate the impact of reformulation on the bioavailability of ecamsule. This proposal to provide in vivo data from ——— Cream combined with the in vitro-permeation study (to address the issue of reformulation) to fulfill the Agency's BA requirements was found acceptable by OCPB at the End-of-Phase 2 meeting held on January 24th, 2001 (meeting minutes in DFS dated 4/4/01). b(4)
The review of ——— has been completed ——— Basically, the clinical pharmacology and biopharmaceutics (CPB) information submitted ——— was found to be acceptable with some labeling recommendations. Therefore, the CPB information previously submitted ——— was not reviewed again since this was already reviewed by this reviewer. In addition the applicant stated that ecamsule has been marketed in Europe since 1996.

However, there is a difference in the age of the proposed population for these three (b) (4) Sunscreen Lotions (6 months and older) compared to ———
The applicant provided some clinical pharmacology information to support administration down to 6 months old. In addition the Phase 3 clinical trials and post-marketing data for (b) (4) Sunscreen Lotions included patients down to 6 months old.

Therefore, this review mainly evaluated the adequacy of the information provided to support the systemic exposure of the (b) (4) Sunscreen Lotions and, the pediatric information provided to support labeling of the (b) (4) lotions for use in children aged 6 months and older. Most of the information provided was for ecamsule, since avobenzone, octocrylene and titanium dioxide are being used within the specified amounts and indications of the OTC monograph.

Systemic Exposure of the (b) (4) Sunscreen Lotions
The totality of the following data indicates that the systemic exposure of ecamsule from the three (b) (4) Sunscreen lotions is minimal:

- The minimal systemic exposure obtained in man, after single and repeated dermal administration of ——— Cream, which contains ecamsule at a concentration of 3% similar to (b) (4) SPF 15 W/R Sunscreen Lotion but higher (3% vs. 2 %) than that of (b) (4) SPF 15 Daily Sunscreen Lotion and (b) (4) SPF 20 W/R Sunscreen Lotion.
- The estimated safety margin of approximately 1000 for ecamsule based on the comparison of the systemic exposure obtained in humans with that obtained in two animal species without causing toxic effects.
- The data from the nonclinical studies indicating that minimal toxic effects were obtained with ecamsule (This was confirmed with pharm/tox reviewer).
- The clinical data showing minimal irritation due to topical application of the three (b) (4) Sunscreen Lotions (This was confirmed with the clinical reviewer).
- The in vitro percutaneous absorption data that suggested that the absorption of ecamsule was comparable between the three sunscreen lotions and ——— cream. Therefore the differences in the concentration of ecamsule (3 % vs. 2 %) and the other formulation differences did not significantly affect the percutaneous absorption of ecamsule.

Pediatric Information to Support Label for Use in Children 6 months and Older

The applicant did not conduct any clinical pharmacology studies with the three (b) (4) Sunscreen lotions in children aged 6 months and older. Due to the larger body surface/body weight ratio of children, that could result in higher systemic exposure, the applicant provided some information to support their line of reasoning that this should not be a safety concern for ecamsule. Basically the applicant provided an estimated safety margin in children that would be greater than 700 based on systemic exposure in humans and animals. This illustrated that there is a significant difference in the margin of safety between adults (1000) and children (> 700). However, its order of magnitude is still relatively large when used under maximal use conditions. In addition, the clinical reviewer (Dr. D. Shetty) concurs that safety is not a concern in the pediatric population. This was based on the fact that the available clinical and post-marketing data reviewed by her did not indicate that there was any specific association of adverse reactions with pediatric use of the (b) (4) Sunscreen lotions containing ecamsule.

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2.1 General Attributes

Physicochemical Properties of the Drug Substances

(b) (4) **SPF 15 Water Resistant (W/R) Sunscreen Lotion** is a white to pale yellow, water-in-oil emulsion. (b) (4) **SPF 15 Sunscreen Daily Lotion and** (b) (4) **SPF 20 W/R Sunscreen Lotion** are both white, water-in-oil emulsions. Inserted below is a summary table of the active ingredients contained in each drug product.

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IND product name	SPF 20 W/R[1]	SPF 15 Daily	SPF 15 W/R
Properties	W/R lotion	Lotion	W/R lotion
Formulation no.	539-106	539-009	760-006
Ingredients:			
Ecamsule	2%	2%	3%
Avobenzone	2%	2%	2%
Octocrylene	10%	10%	10%
Titanium dioxide	2%	--	--

Ecamsule (Trade name outside the USA is Mexoryl® SX) acts as a UVA filter. It has an absorption band from about 290-380 nm with the maximum absorbance at 344 nm. It is a new molecular entity.
Avobenzone acts as a UVA filter. It has an absorption band from about 320-400 nm with the maximum absorbance at 358 nm.
Octocrylene acts mainly as a UVB filter. It has an absorption band from about 250-370 nm with the maximum absorbance at 303 nm.
Titanium Dioxide acts as a physical blocker. It has high opacity and refractive index which enable it to reflect UVB/visible light.

Mechanism of Action:
The mechanism of action of all three (b) (4) lotions is believed to be ultraviolet radiation (UVR) protection by means of absorption, scattering and reflection of incident UVR, thereby reducing the direct penetration and effect of UVR. The applicant's rationale for the combination of the three or four filters was to provide protection across the UVA and UVB light spectrum.

Therapeutic Indication (s):
Prevention of sunburn [redacted] following [redacted] exposure to ultraviolet radiation (UVR).

Proposed Dosage and Route of Administration
(b) (4) **SPF 15 W/R Sunscreen Lotion and** (b) (4) **SPF 20 W/R Sunscreen lotion**

Apply liberally 15 minutes before sun exposure. Reapply as needed or after towel drying, swimming, or perspiring. Children under 6 months of age, ask a doctor.

(b) (4) **SPF 15 Sunscreen Daily Lotion**
Apply evenly to cleansed skin before sun exposure and as needed. Children under 6 months of age, ask a doctor.

2.2 General Clinical Pharmacology

What were the design features of the clinical pharmacology and clinical studies used to support efficacy and safety?

Efficacy: Four pivotal controlled efficacy studies (except NDA 21-501 that had five), and four supportive studies were conducted in support of the product's UVR protection. A brief description of the four pivotal studies is summarized below:
(b) (4) **SPF 15 W/R Sunscreen Lotion and** (b) (4) **SPF 20 W/R Sunscreen Lotion:** Study #'s PEN.820.01, PEN.820.02, PEN.910.01 and PEN.920.01 and 99001.01.COS (for (b) (4) **SPF 15 W/R Sunscreen Lotion only)**

(b) (4) **SPF 15 Sunscreen Daily Lotion:** Study #'s PEN.810.01, PEN.810.02, PEN.910.01 and PEN.920.01

Study #'s PEN.820.01 and PEN.820.02 were water resistant (W/R) sun protection factor (SPF) determination studies of (b) (4) SPF 15 W/R Sunscreen Lotion and (b) (4) SPF 20 W/R Sunscreen lotion. Each study utilized an 8% Homosalate standard sunscreen as the reference therapy and commercially available SPF 15 water resistant sunscreen (Coppertone ® Waterproof Sunscreen SPF 15) as method control. Each study was conducted in healthy volunteers at a single center and had a controlled, randomized, evaluator blind, intra-individual study design. Healthy volunteers were to be between the ages of 18 and 65 years old with fair skin types (I, II, or III) [1] and intact skin in the treatment area. (Reference: 21 CFR Part 352 Subpart D testing Procedure for SPF determination), specifically for determination of water resistant properties (Part 352.76))

Study #'s PEN.810.01 and PEN.810.02 were static sun protection factor (SPF) determination studies of (b) (4) SPF 15 Sunscreen Daily Lotion. Each study utilized an 8% Homosalate standard sunscreen as the reference therapy. Each study was conducted in healthy volunteers at a single center and had a controlled, randomized, evaluator blind, intra-individual study design. Healthy volunteers were to be between the ages of 18 and 65 years old with fair skin types (I, II, or III) and intact skin in the treatment area. (Reference: 21 CFR Part 352 Subpart D testing Procedure for SPF determination).

Study #'s PEN.910.01 and PEN.920.01 were UVA protection factor (PFA) determination studies of (b) (4) SPF 15 W/R Sunscreen Lotion, (b) (4) SPF 20 W/R Sunscreen Lotion and (b) (4) SPF 15 Daily Moisturizing Lotion. Persistent pigment darkening (PPD) was measured in PEN.910.01. The phototoxic erythema, using the 8-methoxypsoralen (8-MOP) method, was measured in PEN.920.01. Each study was conducted in healthy volunteers at a single center and had a controlled, randomized, evaluator blind, intra-individual study design. Healthy volunteers were to be between the ages of 18 and 65 years old, with skin phototypes II, III, or IV (PEN 910.01) or phototypes I, II or III (PEN 920.01) and intact skin in the treatment area.

There is currently no established regulatory testing method for in vivo UVA determination in the Monograph. Study # PEN.910.01 used the minimal PPD method to determine the PFA. In Study # 920.01, the PFA value was based on testing procedures similar to the PPD method except for the use of the photosensitizer 8-MOP. In this case the Minimal Phototoxic Dose (MPD) was determined. The appropriateness of these PFA testing methods is currently being reviewed by the medical reviewer.

The fifth study (#99001.01.COS for NDA 21-501 only) was a Phase 2/3 SPF early formulation screening study which was conducted with (b) (4) SPF 15 W/R Sunscreen Lotion to determine the water-resistant SPF using the same methodology as described above.

Safety: Data to support safety came from the following sources: Phase 1, 2 and 3 clinical studies, post-marketing safety data and a review of the literature.

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[1] Classification of the skin phototypes: Type I – always burns easily; never tans; Type II – always burns easily; tans minimally; Type III – burns minimally; tans gradually; Type IV – burns minimally; always tans well; Type V – rarely burns; tans profusely; Type VI – never burns; deeply pigmented

Phase 1 Studies:
The applicant conducted six Phase 1 dermal tolerance studies in volunteer subjects (3 with all three (b) (4) sunscreen lotions, 3 with Anthelios SP cream) and 3 in vivo pharmacokinetic studies with (b) (4) cream (pending NDA 21-469). The age range of the subjects enrolled in these studies was between 16-91 years old. There was no local safety and PK data on subjects < 16 years old.

Phase 3 Long Term Safety Studies:
Three long-term safety studies (PEN.750.01, PEN.750.02 and PEN.750.03) using the three different (b) (4) formulations were included. These were actual-use studies in healthy individuals and one study (Study RD.06.SRE.18047) was with ——— cream in a compromised subject population i.e. subjects ———

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Study # PEN.750.01 was a Phase 3, multi-center, open-label, safety trial of product usage (daily for up to 12 months) in subjects of any race and skin type, 12 years of age and older. Two hundred and forty eight (248) healthy volunteers were enrolled in the study, including 78 adolescents between 12 and 18 years of age (see table below for a break down of the number of subjects in each age group). Qualified subjects received (b) (4) **SPF 15 Daily Moisturizing Lotion (pending NDA # 21-502)** applied at a dose of 0.5 to 1 mg/cm^2 to the face, neck and hands at least once each morning after washing or cleansing. The applicant stated that while this dose is lower than what is specified in the FDA final monograph (2 mg/cm^2), it was felt that it represented a more realistic dose of product at which related adverse events could be assessed. This realistic dose would enable the assessment of incidences of sunburn during normal long-term human use with outdoor exposure from a safety perspective (***Dr. D. Shetty the medical reviewer considered the applicant's explanation to be reasonable. See medical review for further details***).

Study # PEN.750.02 was a Phase 3, multi-center, open-label, safety trial of product usage (intermittently for up to 12 months) in subjects of any race and skin type 6 months of age and older. Two hundred and forty six (246) healthy volunteers were enrolled in the study, including 179 children 12 years of age and younger (see table below for a breakdown of the number of subjects in each age group). Qualified subjects received (b) (4) **SPF 15 W/R Sunscreen Lotion (NDA # 21-501)** applied at a dose of 0.5 to 1 mg/cm to sun-exposed areas of the skin approximately 15 minutes before each sun exposure.

Study # PEN.750.03 was a Phase 3, two-center, open-label, safety trial of product usage (intermittently for up to 12 months) in subjects of any race and skin type, 6 months of age and older. Eighty (80) volunteers were enrolled in the study, including 25 subjects in the 6 months to 2 years age group, 32 subjects in the 2 years to 6 years age group, and 23 subjects in the greater than 6 years age group. Qualified subjects received (b) (4) **SPF 20 W/R Sunscreen Lotion (pending NDA # 21-471)** applied at a dose of 0.5 to 1 mg/cm^2 to sun-exposed areas of the skin approximately 15 minutes before each sun exposure.
Reviewers Comments (see table below for demographic characteristics):

- *For PEN.750.01 (b) (4) SPF 15 Sunscreen Daily Lotion), there were no children aged between 6 months and 12 years old enrolled in the study. The applicant stated that the safety of this product in children can be verified by looking at the data obtained in Study*

 # PEN.750.02 for (b) (4) *SPF 15 W/R Sunscreen Lotion. While this is a different formulation from the proposed product, it contains a higher concentration (3 % vs. 2%) of ecamsule. (Dr.Shetty, the medical reviewer concurred with this approach).*

- *For PEN.750.02* (b) (4) *SPF 15 W/R Sunscreen Lotion), 179/246 (~70 %) children 6 months to 12 years of age were exposed to* (b) (4) *SPF 15 W/R Sunscreen Lotion and ~ 30 % were between the ages of 6 months and 2 years old.*
- *For PEN.750.03* (b) (4) *SPF 20 W/R Sunscreen Lotion) there were 64 children aged between 6 months and 12 years old enrolled in the study. About 30 % were between the ages of 6 months and 2 years old.*
- *Following discussions with the medical reviewer (Dr. D. Shetty) this reviewer was informed that the number of pediatric patients included was adequate to evaluate safety when combined with the data from 14 additional pediatric (cosmetic) safety use studies conducted outside the US on related sunscreens containing the four UVR filters (ecamsule, avobenzone, octocrylene and titanium dioxide) submitted by the applicant.*

Table 8.6. Summary of Demographic and Baseline Characteristics for Subjects in the Long-Term Safety Studies PEN.750.01, PEN.750.02, PEN.750.03, and RD.06.SRE.18047 (Safety Population)

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	Study Number (%)[1] of Subjects			
Characteristic	**PEN.750.01 (N=248)[2]**	**PEN.750.02 (N=246)[2]**	**PEN.750.03 (N=79)[2]**	**RD.06.SRE. 18047 (N=475)[2]**
Age (years)				
Mean (SD)	35.79 (19.37)	10.98 (12.56)	8.69 (12.05)	45.6 (13.48)
Median	35.44	6.69	3.69	46.0
Range	12.04-83.43	0.5-67.95	0.64-48.15	12-85
Age group (years)				
>0.5 to ≤2	0 (0)	57 (23.17)	24 (30.38)	0 (0)
>2 to ≤6	0 (0)	60 (24.39)	32 (40.51)	0 (0)
>6 to ≤12	0 (0)	62 (25.20)	8 (10.13)	0 (0)
>12 to ≤18	78 (31.45)	24 (9.76)	2 (2.53)	11 (2.3)[3]
>18 to ≤65	145 (58.47)	42 (17.07)	13 (16.46)	428 (90.1)[3]
>65	25 (10.08)	1 (0.41)	0 (0)	36 (7.6)[3]
Sex (n[%])				
Male	58 (23.39)	101 (41.06)	26 (32.91)	83 (17.5)
Female	190 (76.61)	145 (58.94)	53 (67.09)	392 (82.5)
Race (n[%])				
Caucasian	193 (77.82)	193 (78.46)	66 (83.54)	431 (90.7)
Black	23 (9.27)	8 (3.25)	0 (0)	10 (2.1)
Hispanic	26 (10.48)	21 (8.54)	6 (7.59)	25 (5.3)
Asian or Pacific Islander	5 (2.02)	2 (0.81)	4 (5.06)	4 (0.8)
Other	1 (0.40)	22 (8.94)	3 (3.80)	5 (1.1)
Skin phototype (n[%])				
I (always burns easily;never tans)	17 (6.85)	14 (5.69)	6 (7.59)	87 (18.3)
II (always burns easily; tans minimally)	52 (20.97)	96 (39.02)	27 (34.18)	179 (37.7)
III (burns minimally;tans gradually)	90 (36.29)	82 (33.33)	30 (37.97)	153 (32.2)
IV (burns minimally;always tans well)	44 (17.74)	33 (13.41)	12 (15.19)	42 (8.8)
V (rarely burns;tans profusely)	29 (11.69)	17 (6.91)	2 (2.53)	13 (2.7)
VI (never burns;deeply pigmented)	16 (6.45)	4 (1.63)	2 (2.53)	1 (0.2)
Sensitive skin (n[%])				
No	196 (79.03)	207 (84.15)	67 (84.81)	--
Yes	52 (20.97)	39 (15.85)	12 (15.19)	--

What are the clinical or pharmacodynamic end points of the pivotal clinical studies?

The primary efficacy variables were the sun protection factor (SPF) and the UVA protection factor (PFA).

SPF determination: The static SPF studies (PEN. 810.01, PEN.810.02) and the water resistant SPF studies (PEN. 820.01, PEN.820.02 and 99001.01.COS) examined the UVR protection capacities following application of approximately 2mg/cm ^{2} of the product, by measuring the UV-induced clinical response of actinic erythema (sunburn) and determining the respective SPF values of the products and controls. The SPF value was the primary efficacy variable. It was defined as the (MED (minimum erythema dose) of protected skin/MED of unprotected skin). The MED was defined as the quantity of erythema-effective energy required to produce the first perceptible, unambiguous redness reaction with clearly defined borders (minimal erythema) at 22 to 24 hours post-exposure. A 0 (no visible reaction and/or erythema) to 3 (severe/strong erythema with edema) assessment scale was used.

PFA determination: Study PEN.910.01 used the minimal Persistent Pigment Darkening (PPD) method to determine PFA. (b) (4) SPF 15 W/R Sunscreen Lotion, (b) (4) SPF 15 Sunscreen Daily Lotion, or (b) (4) SPF 20 W/R Sunscreen Lotion and the control product (JCIA 2 UVA standard; PFA = 3.75) were applied to two sites on the subject's back and followed by UV exposure from a solar simulator. The quantity of energy required to produce the first perceptible, unambiguous pigmentation reaction with clearly defined borders after 3 hours was recorded as the minimal PPD value for the subject. A four-point scale from 0 (negative, no visible pigment darkening) to 2.0 (moderate clearly defined pigment darkening) was used. The PFA, the primary efficacy variable was defined as (PPD of protected skin/ PPD of unprotected skin).

In PEN.920.01, the PFA of (b) (4) SPF 15 W/R Sunscreen Lotion, (b) (4) SPF 15 Sunscreen Daily Lotion, or (b) (4) SPF 20 W/R Sunscreen Lotion was determined on skin that had been photosensitized with 8-MOP solution for 30 minutes prior to study drug application and was UV irradiated 15 minutes following application. The Minimal Phototoxic Dose (MPD) for each subject was defined as the quantity of effective energy required to produce erythema of grade 1 (defined pigment darkening, i.e., the first perceptible, unambiguous pigment darkening with clearly defined borders) as described on a six-point grading scale (0=no visible pigment darkening and 4.0 = bulla or vesivulation) at 70-74 hours (Day 4) post-irradiation. The PFA, the primary efficacy variable was defined as (MPD of protected skin/MPD of unprotected skin).

What is the systemic exposure of the active ingredients in the three (b) (4) Lotions?

The applicant did not conduct any clinical pharmacology studies with the (b) (4) Sunscreen Lotions. However, the applicant provided the clinical pharmacology data that was obtained for a related drug product, (b) (4) The clinical pharmacology studies for .eam mainly investigated the systemic exposure of ecamsule after topical administration of formulations consisting of concentrations ranging from 2 - 4.95%.

(b) (4)

Since these studies have already been reviewed (signed off in DFS on 3/23/04) and found acceptable they will not be reviewed here again, however a brief overview will be provided as necessary.

Ecamsule:
The applicant stated that the totality of the following data indicates that the systemic exposure of ecamsule from each of the three (b) (4) Sunscreen Lotions is minimal:

1. The minimal systemic exposure obtained in man, after single and repeated dermal administration of ——— Cream, which contains ecamsule at a concentration of 3% similar to (b) (4) SPF 15 W/R Sunscreen Lotion but higher (3% vs. 2 %) than that of (b) (4) SPF 15 Daily Sunscreen Lotion and (b) (4) SPF 20 W/R Sunscreen Lotion. b(4)

Basically, the data was obtained from a maximized exposure study (# 1.CG.03.SRE.2607) conducted in healthy volunteers after single and multiple topical applications of about 15 g of ——— Cream per application (approximately 1 mg/cm^2). The plasma levels of ecamsule were below the quantification limit of the analytical method (1ng/mL) in all but two samples (out of 154 samples) in two subjects. The maximum concentration of ecamsule obtained was 1.95 ng/mL. (4)

The applicant also included data from two supportive studies using different formulations that were supportive of ecamsule having a minimal systemic exposure. The first study was a pharmacokinetic study (Study # V99.1203) using radio-labeled ecamsule as a 2% formulation in healthy volunteers. The systemic absorption after a single topical application, estimated from the radioactivity levels obtained in urine, feces and skin (stratum corneum plus epidermis) was less than 0.1% of the applied dose. In another pharmacokinetic study (Study # V3156) conducted with a 4.95 % ecamsule formulation (not radio-labeled), for a five-day repeated topical application, unchanged ecamsule was not detected in urine.

2. The safety margin of approximately 1000 on the basis of comparing the systemic exposure obtained in humans with that obtained in two animal species. The applicant approximated the safety margin for ecamsule by taking the lower level of quantification in human plasma, 1 ng/mL, as the maximally conceivable level of exposure in man. This value was then compared with the estimated maximal exposure level demonstrated in two species treated orally with ecamsule without showing toxic effects, ~ 1000 ng/mL (This was confirmed with the Pharm/Tox reviewer, Dr. J. Yao), then it was concluded that the safety margin for the systemic exposure of ecamsule is about 1000.
Reviewer's Comments: The actual observed maximum exposure in man was approximately 2 ng/mL. Therefore, the safety margin based on observed data is actually about 500 however, this is still relatively high (applicant stated that Nohynel et. al., 2001, reported that a high margin of safety is considered to be > 100 fold) also, as noted above it represents only 1 of 2 samples out of 154 that had detectable levels.

3. The data from the nonclinical studies indicating that minimal toxic effects were obtained with ecamsule (This was confirmed with pharm/tox reviewer). The pharm/tox reviewer stated that this was based on the following: (1) there was relatively low topical absorption of ecamsule,

(2) low single and repeat dose toxicity, (3) negative genotoxicity, (4) negative dermal carcinogenicity and photocarcinogenicity and (5) no sensitization in guinea pigs.

4. The clinical data showing minimal irritation due to topical application of the three (b) (4) Sunscreen Lotions.

The medical reviewer, Dr. P. Huene was in agreement with this statement. In her review she stated that the dermal safety studies for the (b) (4) SPF 15 W/R Sunscreen Lotion, (b) (4) SPF 15 Daily Sunscreen Lotion and (b) (4) SPF 20 W/R Sunscreen Lotion were adequate to show that there is little or no potential for irritation, phototoxicity, or photosensitization under the conditions of proposed usage. There is however, some potential for sensitization.

Reviewer's Comments: In addition, the medical reviewer (Dr. Shetty) concluded in her review of the total safety data that SPF 15 W/R Sunscreen Lotion and (b) (4) SPF 15 Daily Sunscreen Lotion both have an adequate safety profile

Avobenzone and Octocrylene:
The applicant stated that avobenzone and octocrylene have minimal percutaneous penetration and thus systemic absorption and are considered safe for use as sunscreens in humans as per the Final OTC Sunscreen Monograph. Therefore no major safety concern is expected with their topical use in (b) (4) SPF 15 W/R Sunscreen Lotion. Additionally, the totality of the data (preclinical, *in vitro* and clinical) obtained with Anthelios SP cream indicates that the effect of ecamsule on the systemic absorption of the other active ingredients (octocrylene and avobenzone) used in (b) (4) SPF 15 W/R Sunscreen Lotion is minimal.

2.3 Intrinsic Factors

How does the systemic exposure change with various intrinsic factors?

Pediatrics (Ages 6months to 12 years old):
The applicant is seeking the use of (b) (4) SPF 15 W/R Sunscreen Lotion, (b) (4) SPF 15 Daily Sunscreen Lotion and (b) (4) SPF 20 W/R Sunscreen Lotion in children aged 6 months and older. However, the applicant stated that no clinical pharmacology and biopharmaceutics studies were conducted with children or otherwise compromised patients or patients with a history of sun reactivity (such as PMLE) for the following reasons:

- Very low, mostly undetectable levels of ecamsule were reported even under maximized conditions of exposure in healthy volunteers despite low limits of quantitation
- There is no evidence that the skin exposed to the sun is clinically or histologically different from normal skin concerning the absorption profile of pharmaceutical products
- Permeability of the skin has been described as being relatively constant with respect to age, with no significant differences between the skin of children 6 months and older and adults regarding the penetration of topically applied substances (FDA Enforcement Policy (1997) for OTC marketing of sunscreen products containing avobenzone, Marzulli et. al, 1984 and Schaefer et.al.1996)

Therefore based on the aforementioned, there is no reason to believe that children (6 months and older) should be more susceptible to topical adverse effects of topically applied sunscreens than adults.

Reviewer's Comments:
The above reasons do not address the larger body surface/bodyweight ratio of children when compared to that of adults which could result in the systemic exposure of children to a topically applied sunscreen being somewhat higher than that of a typical adult.

The applicant stated that, even considering higher penetration on compromised skin or higher systemic exposure in children due to a larger body surface/body weight ratio, the overall safety margin for such populations is large, considering that ecamsule was found to be devoid of any toxic potential at the highest dose tested in animals. Considering the body surface to weight ratio to be considerably larger for children, according to Nohynek et al., 2001, the safety margin of adults should be divided by a factor of 1.3-1.4 to estimate the safety margin in children from the percutaneous data. Thus an adult safety margin of 1000 determined for the highest dose sunscreen - ——— Cream, is estimated to be > 700 in children which remains a very high margin of safety. b(4)

Reviewer's Comments: The statement made by the applicant above illustrates that although there is a significant difference in the margin of safety between adults and children, its order of magnitude is still relatively high when used under maximal use conditions. In addition, the clinical reviewer (Dr. D. Shetty) concurs based on the fact that the available clinical and post-marketing data reviewed by her did not indicate that there was any specific association of adverse reactions with pediatric use of the (b) (4) *Sunscreen lotions containing ecamsule.*

Pediatrics (Ages < 6 months old):
The applicant did not ask for a waiver for the use of their products in children aged < 6 months old. However, they did state that they were seeking to comply with the Agency's recommended age limitations for use of sunscreens limiting the age to 6 months and older for use of these new (b) (4) sunscreens. Basically the original OTC review panel concluded that for children less than 6 months of age the mechanisms for metabolizing and excreting drugs absorbed through the skin may not be fully developed therefore, use of topical drugs such as sunscreens may not have the same safety profile in infants under 6 months old.

Reviewer's Comments: At this time it is unclear whether safety studies are needed for the (b) (4) *Sunscreen lotions in Children below 6 months of age. The need for pediatric studies is currently being evaluated by the Division of Pediatric Development.*

2.4 Extrinsic Factors

Drug-Drug Interactions:
The applicant stated that on the basis of chemical stability data, the low absorption of dermally applied ecamsule and the absence of in vitro and in vivo metabolism of ecamsule, the potential for interaction is considered negligible. Consequently, no studies have been conducted.

However, based on the review of the literature by this reviewer, there were two documented drug interactions with sunscreens that relate to alterations in absorption (i.e. a physical drug interaction). They are as follows:

Estradiol topical emulsion (i.e. Estrasorb): In a study conducted to determine the systemic absorption of estradiol it was reported that the application of sunscreens 10 minutes prior to the application of estradiol topical emulsion (i.e. Estrasorb™) increases the exposure to estradiol by approximately 35 %. The application of sunscreen 25 minutes after the application of estradiol topical emulsion increases the exposure to estradiol by approximately 15 %. It was recommended that patients should be advised to separate the application of estradiol topical emulsion and sunscreens as long as possible in order to avoid increased estradiol absorption[2].

Briefly in the study, 7 post-menopausal women applied two 1.74 gram pouches of Estrasorb daily for 25 days to the thighs and calves. On Day 8 through Day 15, SPF15 sunscreen was applied to both thighs and calves 10 minutes prior to Estrasorb application. On Day 16 through Day 23, SPF15 sunscreen was applied to both thighs and calves 25 minutes after the start of Estrasorb application. On day 24 subjects applied Estrasorb alone to both thighs and calves. Subjects were then exposed to direct sunlight for 10 minutes at 10:00 AM and observed for 2 hours for any photosensitivity. Serum hormone levels of estradiol, estrone, estrone sulfate, and FSH were determined over 24 hours on Days 0, 7, 15, and 23.
Reviewer's Comments: Based on the above information it is recommended that patients should be advised in the OTC label to ask their doctor or pharmacist before use if they are using a prescription topical estrogen application, such as Estrasorb

Insect repellants containing diethyltoluamide, DEET: It was reported by Ross et.al. 2004 that application of sunscreens at the same time as insecticides containing diethyltoluamide, DEET may enhance the transdermal absorption of DEET[3]. The authors used a hairless mouse skin model and liquid chromatography/mass spectrometry to quantify the absorption of 20 % DEET (standard) compared with a 9.5 % product with the sunscreens octocrylene, octyl-methopxycinnamate, and benzophenone-3. The sunscreen product was reported to demonstrate a markedly different penetration profile with enhanced DEET permeation. Despite a concentration that is approximately half the standard, the lag time to detection of absorption was reported to have decreased from 30 mins to 5 mins and there was a 3.4 times greater absorption at steady state. It was recommended that this interaction may be of particular significance in children, because of their high surface area to body mass ratios and the health risk of enhanced absorption of DEET. DEET toxicity has manifested as primarily neurotoxic symptoms, including tremor and seizures.

Reviewer's Comments: Based on the above information and the fact that these sunscreens are intended to be used in children down to 6 months old, it is recommended that patients should be advised in the OTC label to ask their doctor or pharmacist before use if they are using insect repellants, such as DEET.

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[2] Estrasorb (estradiol topical emulsion) package insert. Columbia, MD: Novavax, inc.; 2003 Oct.
[3] Ross EA, Savage KA, Utley LJ, et al. Insect repellant interactions: sunscreens enhance DEET (N,N-diethyl-m-toluamide) absorption. *Drug Metab Dispos.* 2004 Aug:32(8):783-5.

2.5 General Biopharmaceutics

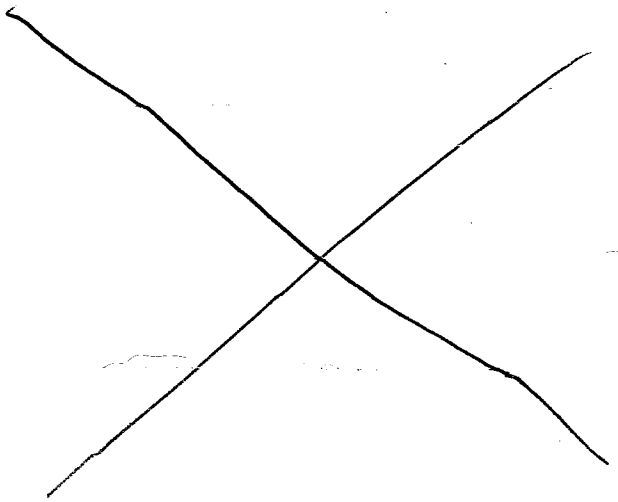
What is the in vivo relationship between the to-be-marketed formulation and the pivotal clinical trial formulation(s)?

The applicant stated that the (b) (4) formulations used in the clinical trial are the same as the proposed commercial formulation. The batch sizes used during clinical development range from 1.5 kg for Phase 2 SPF and UVA studies up to the proposed commercial size of about 1200 kg used for Phase 1 and 3 studies.

What are the variations in formulation between the three (b) (4) Lotion and that of cream?

The table below summarizes the comparison of the composition of the three OTC (b) (4) Sunscreen Lotions and the [redacted] cream.

IND Product Name	SPF 15 Daily Sunscreen Lotion	[redacted]	SPF 15 W/R	SPF 20 W/R	[redacted]
Active Ingredients:					
Ecamsule	2%	3%	2%	3%	
Avobenzone USP	2%	2%	2%		
Octocrylene USP	10%	10%	10%		
Titanium dioxide USP	--	--	2%		
Inactive Ingredients					
Carbomer 940 NF					
Carbomer Copolymer NF Type B					
Cyclomethicone NF					
Dimethicone NF					
Edetate Disodium USP					
Glycerin USP					
Hydroxypropyl Methylcellulose USP					
Isopropyl Palmitate NF					
Methylparaben NF					
Phenoxyethanol Ph. Eur.					
Polyvinylpyrrolidone Eicosene copolymer					
Propylene Glycol USP					
Propylparaben NF					
Stearic Acid NF					
Stearoyl Macrogol glycerides Ph. Eur.					
Stearyl Alcohol NF					
Trolamine NF					
Purified Water USP					



Based on the table above the differences between the (b) (4) lotions and the [redacted] cream are as follows:

(b) (4) **SPF 15 W/R Sunscreen Lotion (NDA 21-501):** [redacted]

(b) (4) **SPF 15 Sunscreen Daily Lotion (NDA 21-502):** Decrease in concentration of ecamsule (2 % vs. 3 %), decrease in concentration of cyclomethicone NF [redacted] and removal of titanium dioxide (5 %) and polyvinnylpyrrolidone eicosense copolymer [redacted]

(b) (4) **SPF 20 W/R Sunscreen Lotion and [redacted] cream (NDA 21-471):** Decrease in concentration of ecamsule (2 % vs. 3 %) and a decrease in the concentration of titanium dioxide (2 % vs [redacted]

What information was provided to bridge the (b) (4) ***Lotions to the*** [redacted] ***cream in order to rely on the Agency's previous findings of efficacy and safety for*** [redacted] ***cream?***

The applicant provided previously submitted [redacted] cream) in vitro percutaneous absorption data to bridge the (b) (4) formulations to [redacted] cream. Data obtained from in vitro percutaneous absorption study [No. 4689] suggested that formulation differences of the three (b) (4) lotions did not significantly affect the percutaneous absorption of ecamsule through human skin. Since this study has already been reviewed and found acceptable, it will not be reviewed again. A brief summary is however, provided.

The in vitro percutaneous absorption study [No. 4689] conducted by the applicant compared the in vitro liberating-penetration of ecamsule incorporated in four different formulations ((b) (4) SPF 15 W/R Sunscreen Lotion, (b) (4) SPF 15 Sunscreen Daily Lotion, (b) (4) SPF 20 W/R Sunscreen Lotion and [redacted] cream) through human skin using diffusion cells. The content of each active ingredient by formulation is presented in the quantitative composition table above. Normally in vitro percutaneous absorption data of this type is NOT considered as part of the review process for a topical dermatological agent. However, since these formulations are intended to be applied to otherwise normal skin as a protectant, the assessment of percutaneous absorption via an in vitro method is considered relevant supportive data.

Basically, a total of 10mg of each formulation (i.e. 200-300 mcg of ecamsule) was applied to a skin surface of 1 cm^2 per cell. There were a total of twelve cells per formulation. The application period was 16 hours under non-occluded conditions. At the end of the 16-hour application period, the concentration of ecamsule was measured in the different skin compartments (stratum corneum, epidermis, dermis, and receptor fluid). The total amounts of ecamsule that penetrated (stratum corneum, epidermis, and dermis receptor fluid) is reproduced in the table below:

[redacted]	2.45 ± 0.58 mcg (0.83% of the applied dose)
(b) (4) Cream SPF 20 (NDA 21-471)	2.01 ± 0.42 mcg (1.12 % of the applied dose)
(b) (4) Cream SPF 15 W/R (NDA 21-501)	2.46 ±0.40 mcg (0.92% of the applied dose)
[No titanium dioxide]	
(b) (4) Lotion SPF 15 (NDA 21-502)	1.41 ± 0.32 mcg (0.69 % of the applied close)
[No titanium dioxide]	

Overall the ***in vitro*** data indicated that the mean amount of ecamsule that penetrated through the skin following the topical application of all four formulations was ≤ 1% (~2.5 mcg). The data indicated that ecamsule was mainly distributed in the stratum corneum (ranging from 0.49 to 0.67 % of the applied dose). The ecamsule concentrations recovered in the dermis were low (ranging from 0.007 % to 0.04 % of the applied dose) irrespective of the formulation. However, the variability was high with the overall variability ranging from 79 % to 97 %. (b) (4) SPF 15

Daily Sunscreen Lotion (containing 2 % of ecamsule) had the lowest absorption (~ 40 % less) of the three (b) (4) lotions when compared with [redacted] cream. Despite the observed differences in percutaneous absorption between [redacted] cream and the three (b) (4) lotions, statistical analyses indicated that there were not significant differences ($p > 0.05$). Therefore, the in vitro data suggests that the mean in vitro percutaneous absorption of ecamsule was comparable between the three (b) (4) Sunscreen Lotions and [redacted] cream despite the differences in the concentrations of ecamsule (3% vs. 2 %) between the four formulations tested. In addition, the presence or absence of titanium dioxide did not appear to affect the percutaneous absorption of the (b) (4) formulations.

b(4)

2.6 Analytical

Were the analytical methods used for the determination of ecamsule in biological fluids validated?

The analytical method used for the determination of ecamsule in plasma was validated and found acceptable (see review for [redacted] cream for details).

3. Labeling Recommendations: See section 1.1 for labeling recommendations

4. Appendix

4.1 Pharmacometrics Consult: None required since there was no PK/PD or POPPK data submitted.

4.2 Proposed labeling(s): [redacted]

b(4)

2 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

b(4)

4.3 Individual Study Reviews: None

4.4 OCPB Filing form

Office of Clinical Pharmacology and Biopharmaceutics *New Drug Application Filing and Review Form*			
General Information about the Submission			
	Information		Information
NDA Number (s)	21-501 21-502 and 21-471	**Brand Name (s)**	(b) (4) SPF 15 Water Resistant (W/R) Lotion Sunscreen, (b) (4) SPF 15 Daily Use Moisturizing Lotion Sunscreen and, (b) (4) SPF 20 Water Resistant (W/R) Sunscreen Lotion
OCPB Division (I, II, III)	DPEIII	**Generic Name (s)**	Ecamsule [Mexoryl® SX] 3%, Avobenzone 2%, and Octocrylene 10%' Ecamsule [Mexoryl® SX] 2%, Avobenzone 2%, and Octocrylene 10%,
Medical Division	OND-540	**Drug Class**	Sun Screen
OCPB Reviewer	Abi Adebowale	**Indication(s)**	To prevent sunburn and skin damage due to chronic sun exposure
OCPB Team Leader	Dennis Bashaw	**Dosage Form**	Lotion
		Dosing Regimen	Apply evenly to cleansed skin before sun exposure and as needed. Children under 6 months of age: ask a doctor (NDA 21-501 & 21-471). Apply evenly to cleansed skin before sun exposure and as needed. Children under 6 months of age: ask a doctor (NDA 21-502)
Date of Submission **Filing Date**	16th May, 2005' 12th May, 2005 27th September, 2005 11th July, 2005 and 10th November, 2005	**Route of Administration**	Topical to skin
Estimated Due Date of OCPB Review	12th December, 2005 and 15th May, 2006	**Sponsor**	L'OREAL USA Products, Inc.
PDUFA Due Date	**12th, March 2006 and 27th June, 2006**	**Priority Classification**	4S

Division Due Date	12th January, 2006 and 27th May, 2006	IND Number	59, 126

Clin. Pharm. and Biopharm. Information

Background and Introduction: (b) (4) SPF 15 W/R and daily use lotion contain three chemical ultraviolet radiation (UVA/UVB) filters. (b) (4) SPF 20 combination product consists of all three UV filters as well as titanium dioxide. The 3 chemical UVR active ingredients include octocrylene, a UVB filter with peak absorbance at about 300 nm; ecamsule, a broad UVA filter with peak absorbance at about 340 nm; avobenzone, a long UVA filter which exhibits peak absorbance at about 360 nm. The applicant stated that there is no new information in (b) (4) NDA item 6, "Human pharmacokinetics and Bioavailability" sections which was previously submitted for review cream. contains , ecamsule 3%. b(4)

The three (b) (4) combination products differs in terms of the indication proposed Sunscreen for (b) (4) and also the population (, down to 6 months for (b) (4) A pediatric waiver request is not included as part of this application. Appropriate pediatric data has been included in item 8, section 11. Also current OTC sunscreen drug product monograph does not yet allow for the use of avobenzone in combination with titanium dioxide in a monograph drug product as proposed with (b) (4) SPF 20. b(4)

b(

In this submission, the applicant has provided an in vitro permeation/liberation study to evaluate the impact of reformulation of the (b) (4) products vs. the ? on the bioavailability of ecamsule. This proposal to provide in vivo data from ' combined with the in vitro-permeation study e to fulfill the Agency's BA requirements was found sufficient by OCPB at the EOP2 meeting held on January 24th, 2001 (meeting minutes in DFS dated 4/4/01).

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Numbers If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X	1		V99.1203 (cream containing 2% of [14C]-ecamsule.
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		1.CG.03.SRE.2607 (used Ecamsule [Mexoryl® SX] 3%, b(4)
multiple dose:	X	2		1.CG.03.SRE.2607, V3156 (cream containing 4.95% of ecamsule, only urinary data was evaluated)
Patients-				
single dose:				

multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Other (in vitro percutaneous absorption study)	X	2		RDS.03.SRE.4689 (evaluated three (b) OTC products including (b) SPF 15 Daily Lotion and also [redacted] Cream) and 16039/G2347 (cream containing 2% of [14C]-ecamsule)
Chronopharmacokinetics				
Pediatric development plan				No systemic exposure data for children aged 6 months to 12 years old was provided. The applicant stated that they are basing their recommended age on the OTC marketing announcement concerning the use of sunscreens. The panel defined adult human skin to be that of individuals older than 6 months of age.
Literature References				
Total Number of Studies		**6**		
Filability and QBR comments				

b(4)

	"X" if yes X	Comments All the Systemic Exposure data included in this submission are the same as that already reviewed in [redacted]. No new information was included in this submission.
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	No	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	What is the relationship between the to-be-marketed formulation and the formulation used in the clinical trials? Does an in vitro study provide an adequate link between the TBMF and the formulation used in the PK study to allow an extrapolation of the systemic exposure data between the two formulations? Acceptable (see EOP2 meeting minutes). Is there adequate pediatric information to support administration down to 6 months old?	
Other comments or information not included above		
Primary reviewer Signature and Date	**Abi Adebowale 07/05/05 and 11/09/05 for filing, 02/03/06 for the review**	
Secondary reviewer Signature and Date		

b(4)

CC: NDA 21-501, 21-502 & 21-471, HFD-850 (P.Lee), HFD-560 (E.Abraham), DCP3 (D. Bashaw, J. Hunt)

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/s/

Abi Adebowale
2/21/2006 11:03:03 AM
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Dennis Bashaw
2/21/2006 12:52:41 PM
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