

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-502

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

1 Executive Summary

L'Oreal has developed — new combination sunscreen drug products namely, []
[] SPF 15 Sunscreen Daily Lotion []
[] for over-the-counter (OTC) use in adults and
children 6 months of age and older.

— of the products [] [] SPF 15 Sunscreen
Daily Lotion, contain three active ingredients (ecamsule, avobenzone and octocrylene) in
[]

— are currently marketed OTC under the Tentative Final Monograph for Sunscreen
Products for Human Use. In the proposed — Sunscreen Lotions, avobenzone, octocrylene
[] — [] are being used within the specified amounts and indications of the OTC
monograph.

Ecamsule is a new chemical entity. Ecamsule was previously studied under IND []

[] the — Sunscreen lotions are intended for children aged 6 months
and older.

Since the clinical pharmacology and biopharmaceutics data provided to
support the marketing of all — Sunscreen Lotions are the same, the — NDAs are
being reviewed together.

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 [] [] SPF 15 Sunscreen Daily 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 [] [] []) 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 _____ 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):

[]

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 _____ ☐
☐ SPF 15 Sunscreen Daily Lotion (NDA 21-502), ☐
☐ 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 _____

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

IND product name	SPF 15 Daily
IND number	59,126
NDA application no.	21-502 ²
Ingredients:	
Ecamsule	2%
Avobenzone	2%
Octocrylene	10%

¹ The proposed drug product of this application.
² The proposed drug product of this application

[]

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).

The review of _____ for _____ cream has been completed and an approvable letter issued on _____. Basically, the clinical pharmacology and biopharmaceutics (CPB) information submitted for _____ was found to be acceptable with some labeling recommendations. Therefore, the CPB information previously submitted with _____ 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 _____ Sunscreen Lotions (6 months and older) compared to _____ cream _____. 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 _____ 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 _____ Sunscreen Lotions and, the pediatric information provided to support labeling of the _____ lotions for use in children aged 6 months and older. Most of the information provided was for ecamsule, since avobenzone, octocrylene _____ are being used within the specified amounts and indications of the OTC monograph.

Systemic Exposure of the _____ Sunscreen Lotions

The totality of the following data indicates that the systemic exposure of ecamsule from the _____ 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 _____ of _____ SPF 15 Daily 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 _____ 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 _____ 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 _____ 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 _____ Sunscreen lotions containing ecamsule.

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2. QBR

2.1 General Attributes

Physicochemical Properties of the Drug Substances

_____] SPF 15 Sunscreen Daily] _____
_____] are both white, _____ Inserted below is a summary table of the active ingredients contained in each drug product.

<u>IND product name</u>	<u>SPF 15 Daily</u>
Properties	Lotion
Formulation no.	539-009
Ingredients:	
Ecamsule	2%
Avobenzone	2%
Octocrylene	10%

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.

[_____]

Mechanism of Action:

The mechanism of action of all _____ 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 [_____] following _____ exposure to ultraviolet radiation (UVR).

Proposed Dosage and Route of Administration

[_____]

_____ **SPF 15 Sunscreen Daily Lotion**

Apply evenly to _____ before sun exposure : _____ 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 [_____], 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:

[_____]

_____ **SPF 15 Sunscreen Daily Lotion: Study #'s** _____ 810.01, _____ 810.02, _____ 910.01 and _____ 920.01

Study #'s — 810.01 and — 810.02 were static sun protection factor (SPF) determination studies of — 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 — 910.01 and — 920.01 were UVA protection factor (PFA) determination studies of — SPF 15 Daily Moisturizing Lotion. Persistent pigment darkening (PPD) was measured in — 910.01. The phototoxic erythema, using the 8-methoxypsoralen (8-MOP) method, was measured in — 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 (— 910.01) or phototypes I, II or III (— 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 # — 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.

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.

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 _____ sunscreen lotions, 3 with _____ cream) and 3 in vivo pharmacokinetic studies with _____). 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 (750.01, 750.02 and 750.03) using the _____ different _____ formulations were included. These were actual-use studies in healthy individuals and one study _____ was with _____ cream in a compromised subject population i.e. subjects with _____

Study # 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 _____ **SPF 15 Daily Moisturizing Lotion (pending NDA # 21-502)** applied at a dose of 0.5 to 1 mg/cm² 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/cm²), 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 # 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 _____ applied at a dose of 0.5 to 1 mg/cm² to sun-exposed areas of the skin approximately 15 minutes before each sun exposure.

Study # 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 _____ applied at a dose of 0.5 to 1 mg/cm² to sun-exposed areas of the skin approximately 15 minutes before each sun exposure.

Reviewers Comments (see table below for demographic characteristics):

- For 750.01 (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

— 750.02 for []

of ecamsule. (Dr. Shetty, the medical reviewer concurred with this approach).

- For — 750.02 [] 179/246 (~70 %) children 6 months to 12 years of age were exposed to [] and ~30 % were between the ages of 6 months and 2 years old.
- For — 750.03 [] 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 — UVR filters (ecamsule, avobenzone, octocrylene [] — []) submitted by the applicant.

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

Characteristic	Study Number (%) ¹ of Subjects			
	— 750.01 (N=248) ²	— 750.02 (N=246) ²	— 750.03 (N=79) ²	— (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 (810.01, 810.02) examined the UVR protection capacities following application of approximately 2mg/cm² 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 910.01 used the minimal Persistent Pigment Darkening (PPD) method to determine PFA. SPF 15 Sunscreen Daily 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 920.01, the PFA of SPF 15 Sunscreen Daily 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 Lotions?

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

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 _____ 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 _____
SPF 15 Daily Sunscreen Lotion _____

Basically, the data was obtained from a maximized exposure study _____ conducted in healthy volunteers after single and multiple topical applications of about 15 g of _____ Cream per application (approximately 1 mg/cm²). The plasma levels of ecamsule were below the quantification limit of the analytical method _____ in all but two samples (out of 154 samples) in two subjects. The maximum concentration of ecamsule obtained was 1.95 ng/mL.

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 _____) 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 # _____) conducted with a _____ 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 _____ 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 _____ SPF 15 Daily 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 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 _____. Additionally, the totality of the data (preclinical, *in vitro* and clinical) obtained with _____ cream indicates that the effect of ecamsule on the systemic absorption of the other active ingredients (octocrylene and avobenzone) used in _____ is minimal.

2.3 Intrinsic Factors

How does the systemic exposure change with various intrinsic factors?

Pediatrics (Ages 6 months to 12 years old):

The applicant is seeking the use of _____ SPF 15 Daily 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 _____ 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.

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 _____ 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 _____ 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.

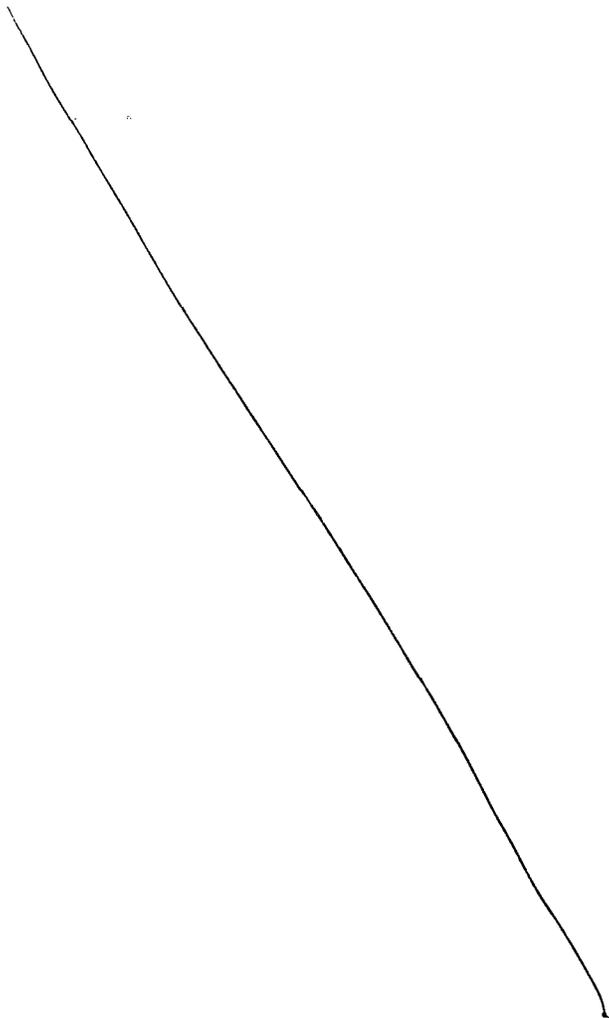
Reviewer's Comments: At this time it is unclear whether safety studies are needed for the _____ Sunscreen lotions in Children below 6 months of age. The need for pediatric studies is currently being evaluated by the Division of Pediatric Development.

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:



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 formulations used in the clinical trial are the same as the proposed commercial formulation. The batch sizes used during clinical development range from _____ for Phase 2 SPF and UVA studies up to the proposed commercial size of about _____ used for Phase 1 and 3 studies.

What are the variations in formulation between the _____ cream?

The table below summarizes the comparison of the composition of the _____ OTC Sunscreen _____ cream.

IND Product Name	SPF 15 Daily Sunscreen Lotion
Active Ingredients:	
Ecamsule	2%
Avobenzone USP	2%
Octocrylene USP	10%
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.	
Propylene Glycol USP	
Propylparaben NF	
Stearic Acid NF	
Stearoyl Macrogol glycerides	
Stearyl Alcohol NF	
Trolamine NF	
Purified Water USP	

Based on the table above the differences between the _____ are as follows:

Peniporo SPF 15 Sunscreen Daily Lotion (NDA 21-502): ecamsule

What information was provided to bridge 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 [redacted] cream. Data obtained from in vitro percutaneous absorption study [redacted] suggested that formulation differences of the [redacted] 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 [redacted] conducted by the applicant compared the in vitro liberating-penetration of ecamsule incorporated in [redacted] different formulations ([redacted] SPF 15 Sunscreen Daily Lotion, [redacted] Sunscreen Lotion [redacted]) 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 cm² 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]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted] Lotion SPF 15 (NDA 21-502)	1.41 ± 0.32 mcg (0.69 % of the applied dose)
[redacted]	[redacted]

Overall the *in vitro* data indicated that the mean amount of ecamsule that penetrated through the skin following the topical application of all [redacted] 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 %. [redacted] SPF 15

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

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): Please note that one of the brand names being proposed by the applicant is _____ Currently DMETS does not recommend the use of the proprietary name _____ Therefore the brand name for this product is still pending.

2 Page(s) Withheld

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

✓ § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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)	21-502	Brand Name (s)	SPF 15 Daily Use Moisturizing Lotion Sunscreen and,
OCPB Division (I, II, III)	DPEIII	Generic Name (s)	Avobenzone 2%, and Octocrylene 10%,
Medical Division	OND-540	Drug Class	Sun Screen
OCPB Reviewer	Abi Adebowale	Indication(s)	To prevent sunburn due to sun exposure
OCPB Team Leader	Dennis Bashaw	Dosage Form	Lotion
		Dosing Regimen	Apply evenly before sun exposure Children under 6 months of age: ask a doctor (NDA 21-502)
Date of Submission	16 th May, 2005 12 th May, 2005 27 th September, 2005	Route of Administration	Topical to skin
Filing Date	11 th July, 2005 and 10 th November, 2005		
Estimated Due Date of OCPB Review	12 th December, 2005 and 15 th May, 2006	Sponsor	L'OREAL USA Products, Inc.
PDUFA Due Date	12 th , March 2006 and 27 th June, 2006	Priority Classification	4S

1 Page(s) Withheld

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

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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		OTC products including SPF 15 Daily Lotion and
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				

	"X" if yes X	Comments
Application filable ?	X	Reasons if the application is <u>not</u> 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 Adebawale 07/05/05 and 11/09/05 for filing, 02/03/06 for the review	
Secondary reviewer Signature and Date		

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

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/s/

Abi Adebawale
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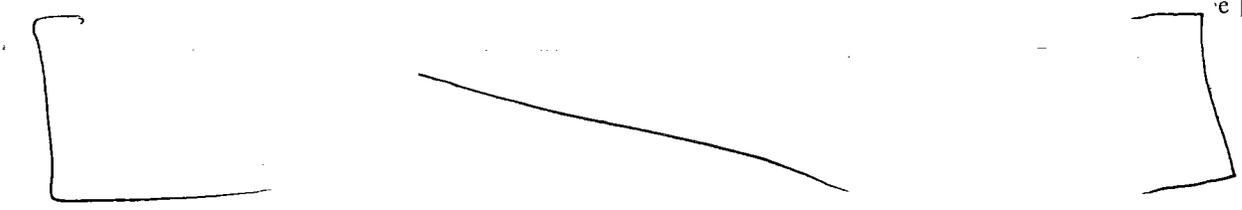
Dennis Bashaw
2/21/2006 12:52:41 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission			
	Information		Information
NDA Number	21-502	Brand Name	— SPF 15 Daily Use Moisturizing Lotion Sunscreen
OCPB Division (I, II, III)	DPEIII	Generic Name	Ecamsule [Mexoryl [®] SX] 2%, Avobenzone 2%, and Octocrylene 10%
Medical Division	HFD-540	Drug Class	Sun Screen
OCPB Reviewer	Abi Adebowale	Indication(s)	To prevent sunburn
OCPB Team Leader	Dennis Bashaw	Dosage Form	Lotion
		Dosing Regimen	Apply evenly _____ before sun exposure _____ Children under 6 months of age: ask a doctor
Date of Submission	12 th May, 2005	Route of Administration	Topical to skin
Filing Date	11 th July, 2005		
Estimated Due Date of OCPB Review	12 th December, 2006	Sponsor	L'OREAL USA Products, Inc.
PDUFA Due Date	12 th , March 2006	Priority Classification	4S
Division Due Date	12 th January 2006	IND Number	59, 126

Clin. Pharm. and Biopharm. Information

Background and Introduction: — SPF 15 contains three chemical ultraviolet radiation (UVA/UVB) filters. 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 — NDA item 6, "Human pharmacokinetics and Bioavailability" sections which was previously submitted for review of pending NDA



	"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		
Isozyme characterization:				
Blood/plasma ratio:				

Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		
multiple dose:	X	2		
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		
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		6		

Filability and QBR comments		
	"X" if yes X	Comments
		
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?
Other comments or information not included above		
Primary reviewer Signature and Date		Abi Adebawale 07/05/05
Secondary reviewer Signature and Date		

CC: NDA — HFD-850 (P.Lee), HFD-560 (E.Abraham), HFD-880 (D. Bashaw, A. Selen)

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/s/

Abi Adebawale
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Dennis Bashaw
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