CLINICAL PHARMACOLOGY REVIEW

NDA Number (s)	22-009
Submission Date(s)	May 31st, 2007
Brand Name(s)	Helioblock ® SX Sunscreen Cream (SPF 40) ***Brand Names are currently being reviewed by DMETS***
Generic Name	Ecamsule 3%, Avobenzone 2%, Octocrylene 10%, and Titanium Dioxide 5 %
Reviewer	Abimbola Adebowale, Ph.D.
Team Leader	Lydia Velazquez, Pharm. D.
OCPB Division	DCP3
OND Division	Office of Nonprescription Products (ONP)
Sponsor	L'Oreal USA Products, Inc. Clark NJ 07066
Relevant IND(s)	59,126 and 57,850
Submission Type; Code	Original NDA for OTC use ; 4S
Formulation; Strength(s)	Cream
Indication	To prevent sunburn and [redacted] following [redacted] exposure to ultraviolet radiation

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1 Executive Summary

L'Oreal has developed a new combination sunscreen product proposed for over-the-counter (OTC) use in adults and children 6 months of age and older. This proposed new drug product is a topical cream containing a combination of three UVA/UVB filters, ecamsule 3%, avobenzone USP 2%, octocrylene USP 10%, and one [redacted], titanium dioxide USP 5 %.

Avobenzone, octocrylene and titanium dioxide are currently marketed OTC under the Final Monograph (21 CFR, part 352) for Sunscreen Products for Human Use. In the proposed Helioblock ® SX Sunscreen Cream, avobenzone, octocrylene and titanium dioxide are being used within the specified amounts and indications of the OTC monograph. The combination of octocrylene with avobenzone or titanium dioxide was included as an acceptable combination of active ingredients in the monograph.

Ecamsule was recently approved in combination with two or three of the above OTC filters in three OTC sunscreen formulations via NDAs submitted by the same sponsor, ([NDA 21-502] approved July 21, 2006, [NDA 21-501] approved October 2, 2006, [NDA 21-471] approved October 6, 2006]). These formulations were approved for the same indication (i.e. of the prevention of sunburn) as Helioblock® SX cream.

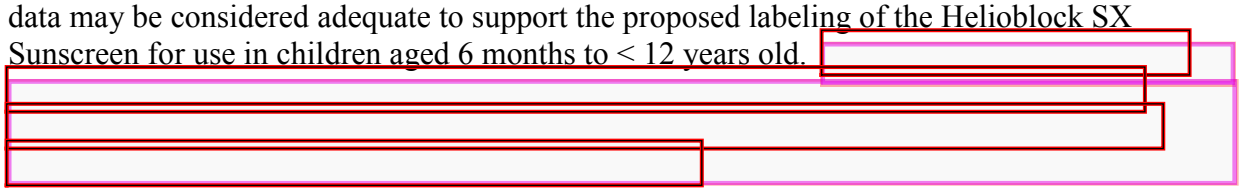
This submission includes the same clinical pharmacology and biopharmaceutics information that had already been reviewed by the Agency in approved NDAs 21-501, 21-502 and 21-471. This includes the in vivo data and the in vitro-permeation studies previously submitted. No approvability issues were raised regarding the Human Pharmacokinetics and Bioavailability Sections of NDA the approval letters for NDA 21-501, 21-502 and 21-471. Please note that "Helioblock SX Sunscreen Cream", "Helioblock SX Cream" and are all used interchangeably throughout this review document. In addition "Ecamsule" and "Mexoryl SX" (the USAN designation trade name for ecamsule) are also used interchangeably in this review.

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 Helioblock SX® Sunscreen 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. 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.

1.2 Phase IV Commitments: None at this time

Please note that following discussions with the medical reviewer (Dr. J. Porres) this reviewer was informed that the clinical safety data obtained from the clinical studies and post-marketing data may be considered adequate to support the proposed labeling of the Helioblock SX Sunscreen for use in children aged 6 months to < 12 years old.



1.3 Summary of Clinical Pharmacology and Biopharmaceutics (CPB) Findings

In this submission, the applicant provided the clinical pharmacology data that was previously submitted for an identical drug product (Helioblock-SX) in pending NDA and the three related sunscreen drug products in NDA 21-501, 21-502 and 21-471. A comparison of the formulations of and other approved and pending topical drug products containing ecamsule, including the NDA number is provided in the table below:

Product Name	**Helioblock® SX Sunscreen Cream and Helioblock® SX Cream**	**Cream**		
Formula No.	760.001	539.106	539.009	760.006
IND No.	57,850	59,126	59,126	59,126
NDA No.	22-009 (Current Application)	21-471 (Approved October 6th, 2006)	21-502 (Approved on July 21st 2006)	21-501 (Approved on October 2nd, 2006)
Active Ingredients				
Ecamsule	3%	2%	2%	3%
Avobenzone	2%	2%	2%	2%
Octocrylene	10%	10%	10%	10%
Titanium dioxide	5%	2%	None	None

[1]W/R=Water resistant and, [2]SPF = Sun Protection Factor

The clinical pharmacology studies for Helioblock® SX 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%. The applicant stated that according to the OTC status of the other three active ingredients, it was not considered necessary to perform specific pharmacokinetic and bioavailability studies on them.

Basically, the clinical pharmacology and biopharmaceutics (CPB) information submitted for [redacted]) was found to be acceptable. Therefore, the CPB information previously submitted with [redacted] was not reviewed again since this was already reviewed by this reviewer. A summary of the CPB data provided to support this application was as follows

A. One pivotal pharmacokinetic study No. 1.CG.03.2607 conducted in healthy volunteers under maximum application conditions of Helioblock SX Cream.
B. Two supportive pharmacokinetic studies conducted with two different cream formulations containing either 2% of [^{14}C]-ecamsule or 4.95% of ecamsule applied topically in healthy volunteers (Study No.V99.1203 and Study No. V3156).
C. Two supportive in vitro penetration studies [No. RDS.03.SRE.4689 and No. 16039/G2347] of ecamsule through human skin.
D. Two supportive in vitro skin penetration studies of avobenzone through human skin and, the effect of titanium dioxide on avobenzone and ecamsule (Study No. 16059 and 16096) along with three relevant published references.
E. Two supportive in vitro penetration Non-GLP studies conducted with a different cream formulation containing either 5% (human and rat skin) or 10% (human skin only) of ecamsule. These studies had no study protocol references, did not use the proposed formulations and were therefore not reviewed because they did not provide any additional information to the clinical pharmacology and biopharmaceutics evaluation.

A summary of the CPB findings obtained from a review of the studies listed under A, B, C and D above, is discussed below.

Pharmacokinetics

Absorption: In a pharmacokinetic study [1.CG.03.SRE.2607] to evaluate the rate of absorption of ecamsule, about 15 g (~1 mg/cm^2) of Helioblock SX Cream was applied as single and multiple (twice daily for 8 days) topical applications, to the trunk, arms, and legs of six male healthy volunteers. For 152 out of 154 (~ 98.7%) of the plasma samples obtained in the study, the plasma concentration of ecamsule was below the limit of quantitation (1 ng/ml) of the assay method used. The lack of quantifiable concentrations in a majority of the samples suggests that systemic exposure to ecamsule following single and multiple topical applications of Anthelios 40 cream is minimal. Two of the samples (~1.3 %) that had quantifiable blood samples (1.93 and 1.8 ng/mL) were obtained in two subjects at sampling time 0 h on days 14 and 15, respectively. The plasma concentration values obtained for the two quantifiable samples indicate that the potential systemic absorption of ecamsule following topical application of Anthelios 40 cream for 8 days results in plasma concentrations < 2 ng/mL, which is also minimal (compared to the highest plasma level (i.e. ~ 1000 ng/mL) at which no toxicity occurred in rats).

Elimination: In a mass balance study [V99.1203], approximately 0.2 g of a cream (different from Helioblock SX Cream) containing [^{14}C]-ecamsule as a 2 % formulation was applied to 100 cm^2 of the forearms of 5 male volunteers, for a period of 4 hours. The amount of radioactivity in the urine (4-24 hrs) as a percentage (Mean ± SD) of the applied dose was 0.011 % ± 0.003. No level of radioactivity above background was detected in blood samples taken up to 168 hours

after application and, in feces samples taken up to 120 hours after application. The estimated percentage of the applied dose available for systemic absorption (skin stripping +urine) was ~ 0.02%. In a urinary excretion study [V3156], approximately 10g of a test formulation (cream different from Helioblock SX Cream) containing 4.95% of ecamsule was applied to the back and front (~3000-5000 cm^2) of 7 male volunteers for 5 days. Ecamsule urine concentrations were below the LOQ (4.9 ng/mL) in all the urine samples collected during 120 h. The recovered amount of ecamsule from urine which was calculated using the LOQ of urinary ecamsule and the voided volume of urine was < 0.002 % of the applied dose of ecamsule. The results of these two studies are limited because they were conducted with formulations that were different from the proposed commercial formulation, and the other three active ingredients were also not present in these formulations. However, the data is consistent with minimal systemic toxicity of ecamsule following topical application.

Biopharmaceutics

In Vitro Percutaneous Absorption: An in vitro percutaneous absorption of [^{14}C]-ecamsule as a 2 % cream, on human skin (mean was ~2 mg/cm^2) to evaluate the cutaneous distribution of [^{14}C]-ecamsule was conducted [Study No. 16039/G2347]. The skin surface was washed at 4 hours, and the cutaneous distribution of [^{14}C]-ecamsule and/or [^{14}C]-derivatives was evaluated at 4 and 24 hours after drug application. At the 4-hour and 24-hour sampling time point, the (mean ± SD) percentage of the applied dose of [^{14}C]-ecamsule that penetrated the skin (stratum corneum, epidermis, dermis and receptor liquid) was 0.36 % ± 0.20 and 0.56% ± 0.35, respectively.

This in vitro study used the same formulation as the one that was used in the in vivo study # V99.1203 therefore a comparison was made between the in vitro data and the in vivo data. Although the in vitro penetration appears minimal (<1%), these values were higher than the systemic exposure obtained (~0.02% of applied dose) with the same formulation in the in vivo study # V99.1203). This data is however limited because it was conducted with a different formulation from the proposed commercial formulation.

The applicant also conducted an in vitro percutaneous absorption study [Study No. 4689] intended to compare the in vitro penetration of ecamsule incorporated in four different formulations through human skin using diffusion cells. One of the formulations was Helioblock SX Sunscreen Cream (to-be-marketed formulation) and the three other ones are the approved [redacted] lotions. A total of 10 mg/cm^2 (i.e. 200-300 mcg of ecamsule) of each formulation was applied to twelve cells. 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 amount of ecamsule recovered from the total skin (i.e. stratum corneum + epidermis + dermis) was ≤ 1 % of the applied dose for Helioblock SX Cream, and the other 3 [redacted] formulations. It appears that the lotion penetrated the least. However, statistical analysis showed that there were no significant differences ($p > 0.05$) between the four formulations. This suggests that the difference in dosage form and the removal of titanium dioxide from two of the products did not affect the in vitro penetration of ecamsule through the skin. Comparison of this data with the previous in vitro data using a lower concentration and, application time, indicates some consistency in that, the amount of ecamsule that penetrated the skin was minimal (<1%).

In another in vitro study (No. 16096) using human skin, the effect of titanium dioxide on the percutaneous absorption of ecamsule and avobenzone was evaluated. Two different o/w emulsion formulations consisting of ecamsule (3%), avobenzone (3.5%) octocrylene (10 %) and Mexoryl XL (3.5 %), with and without titanium dioxide (5 %) included as a pigment were applied at a rate of ~5 mg/cm^2 for a 16 hour duration in a static diffusion cell. The maximum mean percentage of the applied dose of avobenzone and ecamsule recovered in the total skin and receptor fluid was 2.66 (1.41) and 0.15 (0.15), respectively. There was a minimal numerical difference observed in the mean amount that penetrated the skin with or without titanium dioxide however, this difference was not statistically significant ($p > 0.05$). Therefore the results of this study suggest that the presence of titanium dioxide included as a pigment had a minimal effect on the percutaneous penetration of avobenzone and ecamsule. Generally, there was a high variability associated with the in vitro data possibly due to the differences in skin thickness for different donors, which limits comparison across studies. However the data obtained from this study for ecamsule was somewhat consistent (because < 1 % penetrated the skin also) with that obtained in Study No. 4689 that used formulations with the same concentration of ecamsule.

In summary, the results of the CPB studies indicated that systemic exposure to ecamsule is minimal following topical applications. Following single and multiple dose topical applications of Helioblock SX Cream to the trunk, arms, and legs of healthy volunteers, the plasma concentration of ecamsule was < 2 ng/mL. The in vitro data across a number of formulations also indicated that the amount of ecamsule that penetrates human skin in diffusion cells is minimal, supportive of the in vivo data. In addition, a comparison of this data with animal data indicates that the maximum plasma concentration of ecamsule obtained in humans was substantially less than the maximum plasma concentrations of ecamsule (~ 1000 ng/mL) associated with the No Observable Effect Level for Helioblock® SX Cream in the rats. Also all adverse events observed during the human pharmacokinetic studies (although n=6 is small) that were considered possibly related to the drug product were reported as mild and dermatological in nature (e.g. pruritus, eczema).

The non-clinical, in vitro and, clinical data taken all together indicated that the effect of ecamsule on the systemic absorption of the three other active ingredients is minimal, and unlikely to be clinically relevant from a safety perspective. Dr. P. Brown the Pharm/Tox reviewer confirmed that no differences in the systemic and local toxicity of the parameters reported for Helioblock ® SX (tetrad) and Helioblock ® [redacted] (triad) cream were observed in the dermal toxicity studies conducted in different species up to 9 months. This implies that addition of ecamsule does not result in a negative impact on the toxicological profile of Helioblock ® SX cream.

Pediatric Information to Support Use in Children 6 months and Older

There is a difference in the age of the proposed population for this Helioblock SX Sunscreen Cream (6 months and older) for the treatment of sunburn compared to Helioblock SX Cream (12 years and older) for the prevention of PMLE. The applicant provided the same clinical pharmacology information to support administration down to 6 months old that was provided to support the currently approved [redacted] sunscreen formulation. The CP information was found to be adequate for the [redacted] formulations when combined with the clinical safety data that was also provided for the children aged 6 months to 18 years old. However, in this case, the medical reviewer (Dr. J. Porres) informed me that the clinical safety data obtained from the clinical

studies and post-marketing data was not considered adequate to support the proposed labeling of the Helioblock SX Sunscreen for use in children aged 6 months to < 12 years old. Therefore, the proposal at this time is to only label the Helioblock SX Sunscreen Cream for OTC use in children aged 12 years and older.

Abimbola Adebowale, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical, Pharmacology 3, Office of Clinical Pharmacology

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Lydia Velazquez, Pharm.D., Team Leader, Division of Clinical Pharmacology 3, Office of Clinical Pharmacology

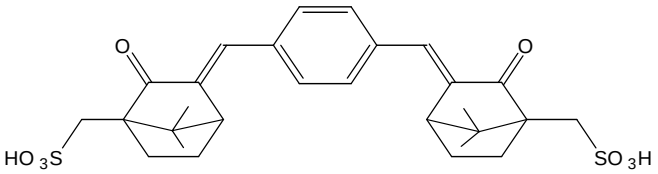
2. QBR

2.1 General Attributes

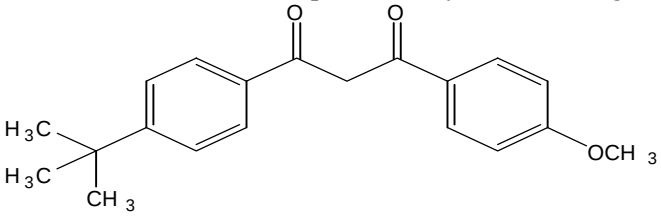
Physicochemical Properties of the Drug Substances:

Helioblock ® SX Sunscreen Cream provides a sun protection factor (SPF) of 40. It is a white, water-in-oil emulsion cream, containing four active sunscreen ingredients: ecamsule (3 %), avobenzone (2 %), octocrylene (10 %) and titanium dioxide (5 %). The properties of these ingredients are as follows:

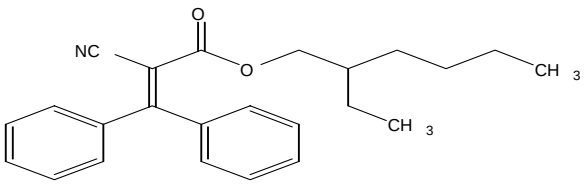
Ecamsule (Trade name outside the USA is Mexoryl® SX) acts as a UVA filter. It has an absorption band from about 290-380 nm with the maximum absorbance at 344 nm. The molecular formula is $C_{28}H_{34}O_8S_2$ and its molecular weight is 562.7. Ecamsule is represented by the following structural formula:



Avobenzone acts as a UVA filter. It has an absorption band from about 320-400 nm with the maximum absorbance at 358 nm. The molecular formula is $C_{20}H_{22}O_3$ and its molecular weight is 310.40. Avobenzone is represented by the following structural formula:



Octocrylene acts mainly as a UVB filter. It has an absorption band from about 250-370 nm with the maximum absorbance at 303 nm. The molecular formula is $C_{24}H_{27}NO_2$ and its molecular weight is 361.5. Octocrylene is represented by the following structural formula:



Titanium Dioxide acts as a physical blocker. It has high opacity and refractive index which enables it to reflect UVB/visible light. The molecular formula is TiO_2, its molecular weight is 79.9 and it is represented by the following structural formula:

O=Ti=O

Mechanism of Action:

The mechanism of action of Helioblock ® SX Sunscreen Cream 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 four filters was to provide protection across the UVA and UVB light spectrum (290-400 nm).

Therapeutic Indication (s):

Prevention of sunburn [redacted] following [redacted] exposure to ultraviolet radiation (UVR).

Proposed Dosage and Route of Administration

Apply evenly 15 minutes before sun exposure. Reapply as needed or after towel drying, swimming, or perspiring. 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: Reproduced in the table below is an overview of the design, response endpoints and number of patients in the Phase 2 and Phase 3 clinical studies:

Overview of Clinical Studies to Support Efficacy			
Study #	**Type of Study**	**Response Endpoints**	**Drug Treatment**
UVB Protection Studies			
1.CG.03.SRE.2612	Sun Protection Factor (SPF) Determination of Helioblock SX cream. Study was designed as a single-center, randomized, controlled, evaluator-blinded, intra-individual comparison in healthy volunteers (Dose = 2 mg/cm^2), (n = 25).	SPF= Minimal Erythema Dose (MED) of Protected Skin/MED of Unprotected skin (FDA 21 CFR part 352)	Helioblock SX cream
1.GUS.05.SRE.18045	SPF Determination of the contribution of each sunscreen active ingredient in the final formulation. Study design was the same as	See above	Helioblock-SX cream (tetrad) and Helioblock SX cream without one of the four filters

	1.CG.03.SRE.2612 (n=41).		(triads)
1.CG.03.2639	SPF Determination following two different application levels (1 mg/cm^2 and 2 mg/cm^2) and determination of the effect of removing ecamsule or both UVA filters on static SPF values to evaluate UVB protection. Study design was the same as 1.CG.03.SRE.2612 (n=25)	See above	Helioblock-SX cream (tetrad) and Helioblock SX cream without ecamsule (E) or ecamsule and avobenzone (E-A)
UVA protection Studies			
1.CG.03.2613	UVA protection determination (UVA-PF). This was a single-center, randomized, controlled, evaluator-blinded, intra-individual comparison study that utilized a parallel-group design, where each subject was treated with Helioblock SX Cream SPF 40 or one triad of its component filters and the control formulation (Japanese Cosmetic Industry Association (JC1A) 2 UVA standard, octyl-methoxtxinnamate 3 %/avobenzone 5 %) in healthy volunteers (Dose = 2 mg/cm^2, N = 60).	UVA-PF = Minimal Persistent Pigment Darkening Dose (MPPD) of protected skin/ MPPD of unprotected skin (by Japan Cosmetic Industry Association)	Helioblock-SX cream (tetrad) and Helioblock SX cream without one of the four filters (triads)
1.CG.03.2614	UVA-PF determination in healthy volunteers. This was a single-center, randomized, controlled, evaluator-blinded, intra-individual comparison study that utilized a within-subject design, where the control (8-methoxypsoralen (8-MOP)) and test formulations were applied to six separate photosensitized sites on the back (Dose = 2 mg/cm^2, N = 14)	UVA-PF=Minimal Phototoxic Dose (MPD) of protected skin / MPD of unprotected skin	Same as study #2613

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. The applicant conducted six Phase 1 dermal tolerance studies in volunteer subjects (3 with all three [redacted] sunscreen lotions, 3 with [redacted] cream (see table below)) and 3 in vivo pharmacokinetic studies with Helioblock-SX cream. 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 1 Studies:

Study #	Type of Study	Response Endpoints	Drug Treatment
Phase 1 Local Tolerance Studies			

1.CG.03.SFR.2604	Irritation and contact sensitization	Cumulative Irritancy Index (C.I.I) = Sum of irritation score/Number of readings.	Helioblock-SX cream (tetrad) and Helioblock SX cream without one of the four filters (triads)
1.CG.03.SRE.2605	Phototoxicity	Skin reaction 15-30 minutes , 24 hours and 48 hours after irradiation (UVA and UVB light) at site of cream application	Same as above
1.CG.03.SRE.2306	Photosensitization	Skin reaction 15-30 minutes , 24 hours and 48 hours after irradiation (total spectrum of UV light) at site of cream application	Same as above

Safety data was also obtained from the Phase2/3 UVA/UVB studies and the supportive studies conducted with Helioblock SX Cream in patients with Polymorphous Light Eruption (PMLE) and those conducted with the approved related [redacted] formulations.

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

UVB Protection Studies: The primary efficacy variable in the UVB protection studies was the static sun protection factor (SPF). The static SPF values were determined as per the testing procedures in the OTC Sunscreen Final Monograph (21CFR Part 352 Subpart D *Testing Procedure for SPF Determination*). The studies were designed to elicit an erythema response (sunburn) following a series of UVR exposures. Prior to product application, the Minimal Erythema Dose (MED) of unprotected skin (control site) was determined for each subject at baseline and used for the determination of UVR doses. The MED was defined as the quantity of UVR exposure 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.

Then 2 mg/cm^2 (or 1 mg/cm^2 in Study 1.GUS.05.SRE.2639) of each test formulation and the control product (Homosalate 8 %) were applied on different sites on the back, following a randomization scheme, at least 15 minutes prior to UV irradiation. The exact series of exposures given to the protected skin was determined by the previously established MED of unprotected skin and the expected SPF of the study drug. The SPF values was calculated from the ratio of the MED of protected and unprotected skin (i.e. SPF = MED of protected skin MED of unprotected skin).

UVA Protection Studies: The primary efficacy variable in the UVA protection studies was the UVA protection factor (PFA) value. In Study # 2613 the PFA value determination was based on testing procedures adopted by the Japanese Cosmetic Industry Association (JCIA) and use the persistent pigment darkening (PPD) as a visual variable. The minimal PPD of unprotected skin (control site) was determined at baseline. Approximately 2 mg/cm^2 of the study product and the control product were applied on different skin sites (~ 35 cm^2 each) followed by UVR exposure from a solar simulator. The test sites were assessed 120, 180 and 240 minutes following UVR exposure by a trained blinded (to test formulation and location of application) examiner. The test sites were assessed according to the following scale 0 (Negative, no reaction pigment darkening),

0.5 (minimal pigment darkening), 1.0 (defined pigment darkening (i.e., the first perceptible unambiguous pigment darkening with clearly defined borders), 2 (moderate pigment darkening). The PPD of the protected and unprotected skin 3 hours following UVR was used for PFA determination (i.e. PFA = PPD of protected skin/PPD of unprotected skin).

In Study # 2614 the applicant stated that PFA value determination was based on testing procedures described in the literature (by Gange et al., and Lowe et al.). the procedure involved determining the Minimal Phototoxic Dose (MPD) on 50 cm^2 test sites topically-photosensitized with 8-methoxypsoralen (8-MOP), one of the areas remained unprotected while the others were protected by Helioblock-SX Cream or its corresponding Triads. The minimal MPD of unprotected skin (control site) was determined at baseline by applying 5 $\mu l/cm^2$ of 8-MOP solution uniformly over the site using a micropipette. The subject was exposed 45 minutes later to a series of UVR exposures. The unprotected site was assessed 72 ± 2 hours (3 days) after UVR. On Day 4, 5 $\mu l/cm^2$ of 8-MOP solution was applied to each of six test sites on the back followed 30 minutes later by test formulations application (2 mg/cm^2 per site). At least 15 minutes after test formulation application, the subjects were exposed to a geometric series (1.25 n) of five UVR exposures, where the middle exposure was selected to yield the expected PFA. The exposed sites were assessed 72 ± 2 hours (3 days) later by a blinded evaluator. The unprotected and test sites were assessed according to the following scale 0 (no reaction, no visible pigment darkening), 0.5 (minimal pigment darkening), 1.0 (defined pigment darkening (i.e., the first perceptible unambiguous pigment darkening with clearly defined borders), 2 (moderate clearly defined erythema), 3.0 (strong erythema, with or without edema), 4.0 (bulla or vesiculation). The MPD of the protected and unprotected skin was used for PFA determination (i.e. PFA = MPD of protected skin/MPD of unprotected skin).

What are the pharmacokinetic characteristics of ecamsule in the drug product?

Absorption***:*** In a pharmacokinetic study [CG.03.SRE.2607] to evaluate the rate of absorption of ecamsule, about 15 g (~1 mg/cm^2) of Helioblock SX Cream was applied as single and multiple topical applications twice daily for 8 days, to the trunk, arms, and legs of six male healthy volunteers. There was a 6-day washout period between single and multiple dosing. Blood samples were taken on day 1 and day 15 at 0, 1, 2, 4, 6, 10, 12, 24, 36, 48, 72, and 96 h post dose and, on the mornings of days 13 and 14 before application. The plasma concentration of ecamsule for 152 out of 154 plasma samples (~98.7 %) obtained in the study was below the limit of quantitation (1 ng/ml) of the assay method used. Two of the samples (~1.3 %) obtained in two subjects had quantifiable blood samples (1.93 and 1.8 ng/mL) at sampling time 0 h on days 14 and 15 respectively. The lack of quantifiable ecamsule concentrations in a majority of the samples suggests a minimal systemic exposure to ecamsule following topical application of Helioblock® SX cream. The plasma concentration values obtained for the two quantifiable samples suggest that the systemic absorption of ecamsule following application of Helioblock SX cream for 8 days results in concentrations < 2 ng/mL. This data also demonstrates that ecamsule accumulation following multiple topical applications is minimal.

In comparison with animal data the maximum plasma concentration obtained in humans was substantially less than the dermal and systemic maximal ecamsule plasma concentrations (~ 500-1000 ng/mL) associated with the No Observable Effect Level (NOEL = 60 mg/kg of ecamsule) for Helioblock® SX in the rats. Although the rat skin and appendages was not the best

model to compare with man, this comparison gives an approximation that is supportive of an unlikely clinical adverse outcome due to the level of ecamsule systemic exposure obtained in humans. Also all adverse events observed during the human pharmacokinetic studies that were considered possibly related to the drug product were reported as mild and dermatological in nature (e.g. pruritus, eczema).

Distribution***:*** Applicant stated that due to the low systemic absorption observed with ecamsule, it was not feasible to study tissue distribution of ecamsule.

Metabolism in vitro/humans: The applicant stated that interspecies metabolism study with hepatic microsomes and an in vivo oral rat study indicated that ecamsule is not metabolized (confirmed with Dr. P. Brown the Pharm/tox reviewer). No metabolism studies were conducted in humans.

Elimination: In a mass balance study [V99.1203], approximately 0.2 g of a cream (different from Helioblock® SX cream) containing [^{14}C]-ecamsule as a 2% formulation was applied to 100 cm^2 of skin on the forearms of 5 male volunteers, for a period of 4 hours. The levels of radioactivity above background were detected in the urine samples of all subjects 4-12 hours and 12-24 hours after exposure. All other sampling times did not contain levels above the background. The total amount of radioactivity in the urine (4-24 hrs) as a percentage (mean ± SD) of the applied dose was 0.011 % ±0.003. No level of radioactivity above background was detected in blood samples up to 168 hours after application and, in feces samples taken up to 120 hours after application. This data indicates that the fraction of the applied dose available for systemic absorption was minimal. In a supportive urinary excretion study [V3156], approximately 10g of a test formulation (cream different from Helioblock® SX cream) containing 4.95% of ecamsule was applied to the back and front (~3000-5000 cm^2) of 7 male volunteers for 5 days. Ecamsule concentrations were below the LOQ (4.9 ng/mL) in all the urine samples collected during 120 h, starting at the first application until 24 hours after the fifth application. This data should be interpreted with caution because the mean recovered amount of ecamsule was ~83 % of the total dose applied. However, this data is suggestive of a minimal systemic absorption of ecamsule from a formulation with a higher concentration applied over an extensive body surface area. Generally, these two studies conducted with different formulations from that proposed were somewhat supportive of minimal systemic exposure of ecamsule following topical application.

What is the effect of ecamsule on the systemic absorption of titanium dioxide?

Due to the monograph status of titanium dioxide, the applicant did not provide any data that determined its systemic exposure following the topical application of [redacted] cream (with or without ecamsule). However the applicant provided in vitro data on the skin penetration of titanium dioxide. They also provided non-clinical and clinical data that evaluated the safety of the triad [redacted]® without ecamsule) and the tetrad [redacted]® cream to support the findings of the in vitro data.

The in vitro data was a publication by **Schultz et al. 2002**[1]. The authors assessed the distribution of three oil/water emulsions containing 4% of different types of micronised (particle size ranging from 20 –100 nm) titanium dioxide each. The emulsions were applied for 6 hours without occlusion on the forearm of healthy human volunteers at a dose of 4 mg/cm^2. Punch biopsies (2

[1] Schulz J, Hohenberg H, Pflucker F, Gartner E, Will T, Pfeiffer S, Wepf R, Wendel V, GersBarlag H, Wittern KP. Distribution of sunscreens on skin *Adv. Drug Delivery Reviews*, **54 Suppl 1**:2002;S157-S163

mm diameter) were subsequently taken from the center of the respective test areas and prepared for light microscopy or transmission electron microscopy visualization and investigation. Light and electron microscopy showed that the titanium dioxide particles were located mainly on the outermost layer of the human stratum corneum. Titanium dioxide was not detected in deeper stratum corneum layers, the human epidermis, and dermis. Therefore this data was suggestive of minimal to non-existent penetration of titanium dioxide through the skin. In addition there were no differences observed in the toxicological and safety profile of the triad (without ecamsule) and the tetrad (with ecamsule) indicating that ecamsule is unlikely to have an effect on the systemic exposure of titanium dioxide that is clinically relevant.

What is the effect of ecamsule on the systemic absorption of octocrylene?

Due to the monograph status of octocrylene, the applicant did not provide any data that determined its systemic exposure following the topical application of ® cream (with or without ecamsule). However the applicant provided in vitro data on the skin penetration of octocrylene. They also provided non-clinical and clinical data that evaluated the safety of the triad (® without ecamsule) and the tetrad ® cream to support the findings of the in vitro data.

Jiang et al, 1999[2] examined the skin penetration of octocrylene and three other sunscreen agents in six commercial products indicated for children and adults. The study was performed in vitro using a Franz type diffusion cell. Only one of the products contained octocrylene and the concentration was 70 g/L (~7%). The sunscreen product was applied to human skin (surface area = 1.13 -1.23 cm^2). Following 8-hr topical applications of the products it was reported that no octocrylene was detected in the receptor fluid suggesting that penetration through the skin was minimal to non-existent.

Potard et al, 2000[3] examined the percutaneous absorption of 5 UV filters, in vitro, by fresh human dermatomed skin (350 ± 50 micrometers thickness), after exposure times of 30 minutes and 16 minutes. One of the UV filters examined was octocrylene incorporated in an oil/water emulsion and, 3mg/cm^2 of the formulation were applied on the skin (1.86 cm^2). The mean quantity of all the filters (except benzophenone-3) in the receptor fluid was nil or close to zero. This data also indicates that octocrylene penetration through the skin is minimal to negligible. In addition there were no differences observed in the toxicological and safety profile of the triad (without ecamsule) and the tetrad (with ecamsule) indicating that ecamsule is unlikely to have an effect on the systemic exposure of octocrylene that is clinically relevant.

What is the effect of ecamsule on the systemic absorption of avobenzone?

Avobenzone is already the subject of an approved NDA (19-459) that uses a higher concentration (3% vs. 2%) than that proposed in Helioblock® SX cream. Therefore, there is already an existing safety database for avobenzone in the Agency that covers the proposed concentration in Helioblock SX cream. The applicant stated that in vitro and, mass balance (in vivo) additional data for avobenzone supported minimal percutaneous absorption and thus

[2] Jiang R, Roberts MS, Collins DM, Benson HAE. Absorption of Sunscreens across Human Skin: An Evaluation of Commercial Products for Children and Adults. *Br. J. Clin. Pharmacol*., 1999, **48**:635-637.

[3] Potard G, Laugel C, Schaefer H, Marty J-P. The stripping technique: in vitro absorption and penetration of five UV filters on excised human skin. *Skin Pharmacol. Appl.Skin Physiol*. 2000; **13**:336-344

systemic absorption of avobenzone. Since the mass balance data was not conducted with the proposed commercial formulation it was not reviewed.

In one in-vitro study [Study No. 16059], human skin samples were isolated in a static Franz diffusion cell. Four different formulations of avobenzone in different vehicles were applied at a rate of ~5 mg/cm^2. The absorption and penetration of avobenzone was determined after 16 hours of application. The percentage of the applied dose of avobenzone that penetrated into the receptor liquid was minimal (<0.04%) and comparable for all the formulations. The mean ±SD percentage of the applied dose of avobenzone that was recovered from the total skin and receptor liquid ranged from 1.35±0.92 to 8.77 ± 2.76 %.

In the second in vitro study [Study No. 16096], a similar methodology as in Study 16059 was used, with two different O/W emulsion formulations consisting of ecamsule (3%), avobenzone (3.5%) octocrylene (10 %) and Mexoryl XL (3.5 %), with and without titanium dioxide (5 %) included as a pigment. The absorption and penetration of avobenzone and ecamsule were determined after 16 hours of application. The mean ± SD percentage of the applied dose of avobenzone recovered in the total skin and receptor fluid was 1.98 ± 0.90 and 2.66 ± 1.41 with and without the titanium dioxide respectively. These values were within the range of that obtained in study 16096 above that evaluated formulations containing avobenzone alone. In addition the percentage of the applied dose of avobenzone that penetrated into the receptor liquid was minimal (<0.02%) and comparable for both the formulations. Therefore the data suggests that the UV filters including 3% ecamsule combined with avobenzone in both formulations tested, had a minimal effect on the skin penetration of avobenzone. In addition the non-clinical and clinical data that indicated no observed differences in the toxicological and safety profile of the triad (without ecamsule) and tetrad (with ecamsule) were supportive of this data.

What is the effect of ecamsule on the systemic exposure of a combination of avobenzone and octocrylene?

Modification of skin barrier function:
Clinical and non-clinical observations indicate that any modification of the skin barrier function due to the presence of ecamsule is unlikely to be of any clinical relevance. Following discussions with Dr. P Brown [Pharm/Tox] reviewer and Dr. P. Huene [Medical reviewer] it was concluded that no skin irritation was induced by Helioblock ® SX Cream in either toxicological studies or clinical local tolerance Phase 1 studies. For the toxicological studies there was no difference between the observations obtained with Helioblock ® SX cream and Helioblock® Cream (without ecamsule). For the Phase 1 irritation and contact sensitization (1.CG.03.SPR.2604) studies, Helioblock® SX cream and its corresponding triads were applied repeatedly to the skin of healthy volunteers. The results of this study were adequate to conclude that there is little or no potential for significant irritation or contact sensitization.

Systemic Toxicity
The non–clinical systemic toxicological data indicated that the presence of ecamsule did not result in a negative change in the systemic toxicity of the three OTC UV filters combined together. Following discussions with Dr. P. Brown the Pharm/Tox reviewer it was confirmed that no differences in the systemic and local toxicity of the parameters reported for the

Helioblock ® SX and Helioblock ® [redacted] cream (without ecamsule) were observed in the dermal toxicity studies conducted in different species up to 9 months.

The clinical safety profile and adverse events incidence reported with the complete formulation (Helioblock ® SX Cream) are identical to those of triads excluding either ecamsule or avobenzone in local tolerance studies conducted in healthy volunteers or in Phase 2 & 3 controlled studies in healthy volunteers or patients affected by PMLE. However, following discussions with Dr. P. Huene (the medical reviewer) it was concluded that for the Phase 2 studies the number of subjects was so small that they might not have been able to detect a difference.

In conclusion the data of the in vitro, non-clinical and clinical data provided by the applicant indicate that the effect of ecamsule on the systemic absorption of the other three active ingredients (octocrylene, avobenzone and titanium dioxide) used in Helioblock ® SX cream formulation is minimal and, unlikely to be clinically relevant from the safety perspective. .

2.3 Intrinsic Factors

How does the systemic exposure change with various intrinsic factors?

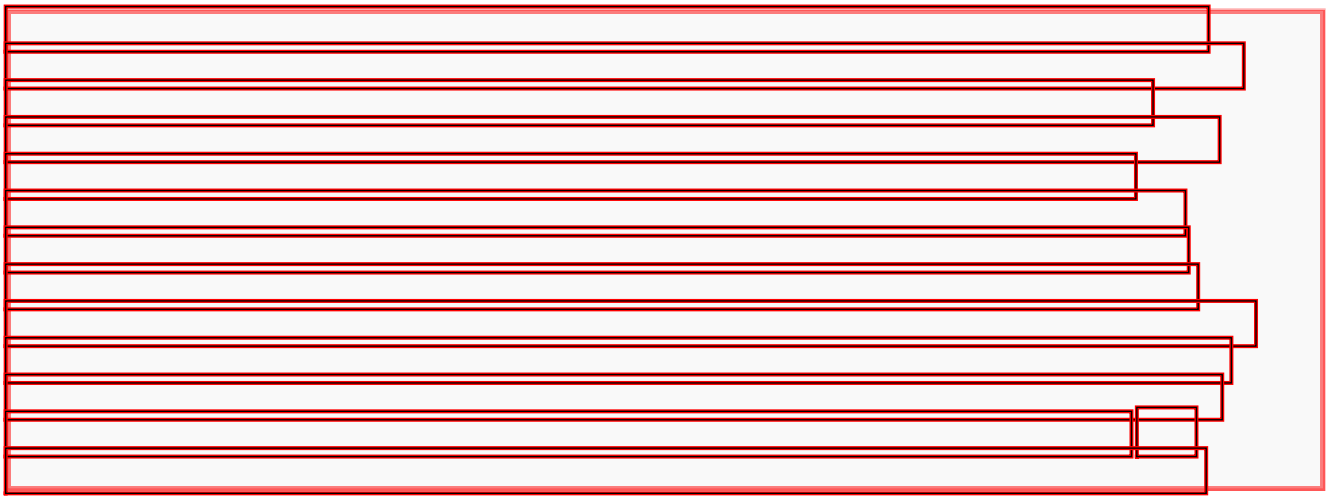
Pediatrics (Ages 6 months to 12 years old):
The applicant is seeking the use of Anthelios cream in children aged 6 months and older. The applicant did not conduct any PK studies in children Aged 6 months to <18 years old. However, the applicant provided the same clinical pharmacology information to support administration down to 6 months old that was provided to support the currently approved [redacted] sunscreen formulation (NDAs 21-471, 21-501 and 21-502). The applicant also provided clinical safety data in children aged 6 months to 18 years old from related formulations (i.e. approved [redacted] sunscreen formulations and some unapproved formulations).

Clinical Pharmacology Information:
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)

The applicant also 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 [redacted] Cream, is estimated to be > 700 in children which remains a very high margin of safety.



Pediatrics (Ages < 6 months old):
A partial pediatric waiver request for infants < 6months of age is included as part of this application. Please note that similar requests for a waiver of testing in the infant age group of 6 months of age or less have been granted by the Agency for the related [redacted] sunscreen formulations approved via NDA 21-502, NDA 21-501 and NDA 21-471.

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). Please note that these interactions are also included in my review for the approved [redacted] sunscreen formulations (NDAs 21-501, 21-502 and 21-471). They are as follows:

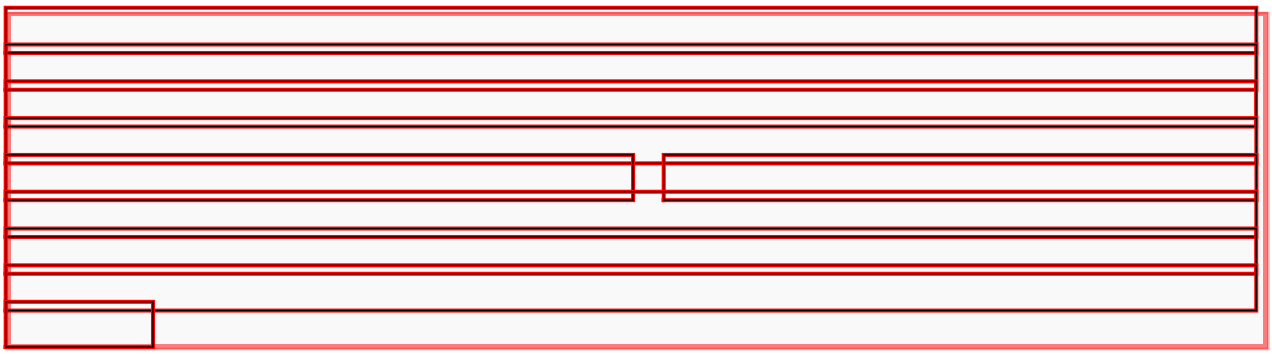
Estradiol topical emulsion (i.e. Estrasorb): In a study conducted to determine the systemic absorption of estradiol it was reported that the application of sunscreens 10 minutes prior to the application of estradiol topical emulsion (i.e. Estrasorb™) increases the exposure to estradiol by approximately 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[4].

[4] Estrasorb (estradiol topical emulsion) package insert. Columbia, MD: Novavax, inc.; 2003 Oct.

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[5]. The authors used a hairless mouse skin model and liquid chromatography/mass spectrometry to quantify the absorption of 20 % DEET (standard) compared with a commercially marketed sunscreen product that had 9.5 % DEET and the following sunscreens: octocrylene, octyl-methopxycinnamate, and benzophenone-3. The authors reported that there was substantial penetration of the 20% DEET standard. Despite a lower (9.5%) DEET content, the commercially marketed sunscreen formulation had a 6-fold more rapid detection of absorption (5 versus 30 min) and 3.4-fold greater penetration of DEET 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.

Based on the documented interactions in the literature between sunscreens and, estradiol topical emulsion (i.e. Estrasorb) and DEET, the following label is recommended:
"Ask your doctor or pharmacist before use if you are using a topical prescription estrogen product, such as Estrasorb or a non-prescription insect repellant".



[5] 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

Was the formulation of [redacted] cream identical to that of Helioblock SX Sunscreen cream?

Yes, they are identical with the same formulation # 760.001 and drug components and composition. This was confirmed with the chemistry reviewer (Dr. Christopher Hough).

Table of Drug Product Qualitative and Quantitative Formula:

Ingredient	% (w/w)	mg/g
Drug Substances:		
Avobenzone	2.00	20.0
Ecamsule[2]	3.00	30.0
Octocrylene	10.00	100.0
Titanium dioxide	5.00	50.0
Excipients:		
Carbomer 940		
Carbomer Copolymer [redacted], Type B[3]		
Cyclomethicone		
Dimethicone		
Edetate Disodium		
Glycerin		
Hydroxypropyl Methylcellulose		
Isopropyl Palmitate		
Methylparaben		
Phenoxyethanol		
Polyvinylpyrrolidone/Eicosene Copolymer		
Propylene Glycol		
Propylparaben		
Stearic Acid		
Stearoyl Macrogolglycerides		
Stearyl Alcohol		
Trolamine		
Purified Water		

[redacted]

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

The formulation (# 760.001) used in the clinical trials is the same as the proposed commercial formulation.

What is the in vitro percutaneous absorption of Helioblock SX cream and how does this relate to the in vivo systemic exposure?

An in vitro percutaneous absorption of [^{14}C]-ecamsule as a 2 % cream, on human skin (mean was ~2 mg/cm^2) to evaluate the cutaneous distribution of [^{14}C]-ecamsule was conducted [Study No. 16039/G2347]. The skin surface was washed at 4 hours, and the cutaneous distribution of [^{14}C]-ecamsule and/or [^{14}C]-derivatives was evaluated at 4 and 24 hours after drug application. At the 4-hour and 24-hour sampling time point, the (mean ± SD) percentage of the applied dose

of [^{14}C]-ecamsule that penetrated the skin (stratum corneum, epidermis, dermis and receptor liquid) was 0.36 % ± 0.20 and 0.56% ± 0.35, respectively.

This in vitro study used the same formulation as the one that was used in the in vivo study # V99.1203 therefore a comparison was made between the in vitro data and the in vivo data. Although the in vitro penetration appears minimal (<1%), these values were higher than the systemic exposure obtained (~0.02% of applied dose) with the same formulation in the in vivo study # V99.1203). This data is however limited because it was conducted with a different formulation from the proposed commercial formulation.

The applicant also conducted an in vitro percutaneous absorption study [Study No. 4689] intended to compare the in vitro penetration of ecamsule incorporated in four different formulations through human skin using diffusion cells. One of the formulations was Helioblock SX Sunscreen Cream (to-be-marketed formulation) and the three other ones are the approved [redacted] lotions. A total of 10 mg/cm^2 (i.e. 200-300 mcg of ecamsule) of each formulation was applied to twelve cells. 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 amount of ecamsule recovered from the total skin (i.e. stratum corneum + epidermis + dermis) was ≤ 1 % of the applied dose for Helioblock SX Cream, and the other 3 [redacted] formulations. It appears that the lotion penetrated the least. However, statistical analysis showed that there were no significant differences ($p > 0.05$) between the four formulations. This suggests that the difference in dosage form and the removal of titanium dioxide from two of the products did not affect the in vitro penetration of ecamsule through the skin. Comparison of this data with the previous in vitro data using a lower concentration and, application time, indicates some consistency in that, the amount of ecamsule that penetrated the skin was minimal (<1%).

The applicant also conducted an in vitro percutaneous absorption study [No. 4689] intended to compare the in vitro liberating-penetration of ecamsule incorporated in four different formulations through human skin using diffusion cells. One of the formulations was Helioblock® SX cream (to be marketed formulation) and the three other ones were approved formulations ([redacted] cream (2 different ones) and [redacted] lotion). The content (%) of each active ingredient by formulation is presented in Tale F.1.2.1 below.

Table F.1.2.1 – Study No. RDS.03.SRE.4689
Active Ingredients Content in the Formulations Tested

	Ecamsule (UVA filter)	Octocrylene (UVB filter)	Avobenzone (UVA filter)	Titanium Dioxide (UVB filter)
Helioblock® SX [760.001 [redacted]	3	10	2	5
[redacted] Cream [760.006 [redacted]	3	10	2	0
[redacted] Cream [539.106 [redacted]	2	10	2	2
[redacted] Lotion [539.009 [redacted]	2	10	2	0

A total of 10mg/cm^2 (i.e. 200-300 mcg of ecamsule) of each formulation was applied to twelve cells. 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).

Results of the In Vitro study #RDS.03.SRE.4689:

Product Name	**Helioblock® SX Sunscreen Cream**	**SPF 20 W/R[1]**	**SPF 15 Daily Use lotion**	**W/R Cream**
Formula No.	760.001	539.106	539.009	760.006
Ecamsule Content	3%	2%	2%	3%
Total Penetrated[1] µg of ecamsule % of applied dose	 2.45 ± 0.58 0.83 %	 201 ± 0.42 1.1 %	 1.41 ± 0.32 0.69 %	 2.46 ± 0.40 0.92 %

[1]Total Penetrated = [Total Skin (i.e. stratum corneum + epidermis + dermis) +receptor fluid]

As shown in the table above, the in vitro data demonstrated that less than 1% (~2.5 mcg) of ecamsule penetrated through the skin following topical application of Helioblock-SX cream. The in vitro data was somewhat consistent with the in vivo data in that the amount absorbed was minimal (<1%). However, there was a considerable amount of variability associated with the in vitro data (as indicated by the large 90 % CI's obtained, see table below) and also possibly due to the differences in skin thickness for different donors. The statistical analysis showed that there were no significant differences ($p > 0.05$) between the other three formulations when compared to Helioblock-SX cream, suggesting that the removal of titanium dioxide from one of the products did not affect the in vitro penetration of ecamsule through the skin.

Statistical data for quantities that penetrated through the skin (dermis, epidermis and stratum corneum)

Formulation Comparisons*	Ratio	90% CI	p-value
A vs. B	1.23	0.72, 2.11	0.513
A vs. C	0.85	0.49, 1.46	0.608
A vs. D	1.58	0.92, 2.71	0.158

*A=Helioblock SX cream, B , C , D =

Generally for both in vitro studies ecamsule was found to remain primarily on or in the stratum corneum and penetrate poorly into the underlying tissues.

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 table below).

Assay Method	HPLC/MS after solid phase extraction (SPE)
Analytical Site	Galderma Research & Development Sophia Antipolis-France
Compound	Ecamsule
Internal Standard	
Matrix	Human Plasma
Accuracy (between –day)	88 – 115 %
Precision (CV%) within-day	< 11% (raw data not provided)
Standard curve range	1 – 50 ng/mL (accuracy ranged from 88-115%) (r > 0.9992)
Sensitivity (LOQ)	1 ng/mL (Accuracy = 99.8 to 106.6 %)

Selectivity	No chromatograms provided, applicant stated specificity is correct.
Stability	No degradation of ecamsule was observed after 12 weeks at a temperature ≤ -16 °C and after four freeze/thaw cycles. (raw data not provided)

3. Labeling Recommendations: None

4. Appendix

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

4.2 Proposed labeling(s): The brand name for this product is still pending. Inserted below is a copy of the Drug Facts Box product labeling:

Drug Facts

Active ingredients ..... ***Purpose***
Avobenzone 2% ..... Sunscreen
Ecamsule 3% ..... Sunscreen
Octocrylene 10% ..... Sunscreen
Titanium dioxide 5% ..... Sunscreen

Uses

- ·helps prevent sunburn
- higher SPF gives more sunburn protection
- helps provide protection from UVA rays (short and long wavelengths)

Warnings
For external use only

Do **not use** on

- broken skin
- serious burns

When using this product

- keep out of eyes, Rinse with water to remove.

Stop use and ask a doctor if

- rash or irritation develops and lasts

Keep out of reach of children, if swallowed,
get medical help or contact a Poison Control Center right away.

Directions

- apply evenly 15 minutes before sun exposure

- reapply as needed or after towel drying, swimming, or perspiring
- children under 6 months of age, ask a doctor

Inactive ingredients carbomer 940, carbomer copolymer Type B, cyclomethicone, dimethicone, edetate disodium, glycerin, hydroxypropyl methylcellulose, isopropyl palmitate, methylparaben, phenoxyethanol, polyvinylpyrrolidone/eicosene copolymer, propylene glycol, propylparaben, purified water, stearic acid, stearoyl macrogolglycerides, stearyl alcohol, trolamine

Questions ?
X-XXX~XXX-XXXX
Monday -Friday (9 am to 5 pm, EST)

4.3 Individual Study Reviews:

Study Abstract Sheet: Study No. 1.CG.03.SRE.2607 (Pivotal)

Name of Investigational P (Helioblock SX Cream)	**Name of Active Ingredient:** 3% Ecamsule + 10% Octocrylene + 2% Avobenzone + 5% Titanium Dioxide	**Indication:** Prevention of Polymorphous Light Eruption (PMLE)
Title of Study: Maximized Exposure Pharmacokinetic Evaluation of Ecamsule following Single and Multiple topical administration of Helioblock ® SX Cream in Healthy Volunteers		
Principal Investigators: Dr. S. Lens and Dr. S. De Bruyn		
Study Centers: SGS Biopharma S.A., Clinical Research Unit, A.Z. Stuivenberg, Lange Beeldekensstraat, 267 B-2060 Antwerpen Belgium		
Objectives: The purpose of this study was to investigate the rate of absorption, the pharmacokinetics and the safety of ecamsule following topical administration of Helioblock ® SX Cream in healthy human volunteer subjects.		
Design of Study: Phase I, single center, open-label, one treatment, maximal exposure study		
Study Schedule: August 8th-September 9th, 1998 (Analysis was 23rd November-8th December, 1998).		
Study Population Demographics: 6M, Age Range 23-55, All Caucasian, Wt = 63.3 – 74.8 kg, Height=167-187 cm **Study Population Characteristics:** Skin phototype: II (1 subject) burns easily, tans minimally and III (5 subjects) burns moderately, tans gradually		
Investigational Product: Helioblock ® SX Cream, Batch No. 760.001/2F7		
Dosing Regimen, Mode of Administration and Treatment Duration: 15 g (range 14.9-15.1g) per application (~1 mg per square centimeter). Topical application to the whole body surface (trunk, arms, and legs). Single whole body application on Day 1 by applicant, followed by 6 days wash out period. Then twice daily (6 ±2 hours apart) whole body applications by local study coordinator for 8 days (Days 7-14) and the final application on the morning of Day 15. (Similar regimen and duration as Phase 2 study # 2616 which was twice daily for 6 days). *Reviewer's Comment: Application by study coordinator during multiple dose phase does not represent clinical use conditions*		
Pharmacokinetic Sampling and Handling: Blood samples on Day 1 and Day 15 at 0, 1, 2, 4, 6, 10, 12, 24, 36, 48, 72 and 96 h post dose, and one sample on the morning of day 13 and 14. **Analytical Methods**: LC/MS, LOQ = 1ng/mL **Pharmacokinetic and Statistical Analysis:** Descriptive statistics on plasma concentrations after single and repeated dose administration.		
Summary Conclusions: Ecamsule plasma concentrations were below the limit of quantification (1 ng/mL) for 98.7 % (152/154) of the samples. Two samples (1.3 %) in two subjects (# 2 and 3) had quantifiable levels. Mean (first 1.93 ng/mL and second 1.95 ng/mL assay) value was approximately 1.94 ng/mL for subject 3 at time 0 on day 14, and 1.8 ng/mL (first assay, second assay was BLQ) for subject 2 at time 0 on day 15. The result of this		

sample should be interpreted with care as no levels were found during the second assay. Two blood samples were missing (subject 1-day 15 @ 10 h post dose, subject 3-day 13 @ 0 h). The overall percutaneous absorption is therefore thought to be minimal under the maximal exposure conditions investigated.
Safety: A total of 18 adverse events of mild intensity were reported during the trial. Two of them (exacerbation of folliculitus on the back and papules on shoulder) were considered probably related to the study drug. Four others (2 cases of pruritus and 2 cases of eczema) were graded as possibly related. The others (dizziness and headaches) were considered unlikely to be related to the study drug.

Assay Method	HPLC/MS after solid phase extraction (SPE)	
Analytical Site	Galderma Research & Development Sophia Antipolis-France	
Compound		Ecamsule
Internal Standard		
Matrix		Human Plasma
Accuracy	***Between-Day***	88 – 115 %
Precision (CV %)	***Between-Day***	< 11% (raw data not provided)
Standard curve range		1 – 50 ng/mL (Accuracy ranged from 88-115%) (r > 0.9992)
Sensitivity (LOQ)		1 ng/mL (Accuracy = 99.8 to 106.6 %)
Selectivity		No chromatograms provided, applicant stated specificity is correct.
Stability		No degradation of ecamsule was observed after 12 weeks at a temperature ≤ -16 °C and after four freeze/thaw cycles. (raw data not provided)
Reviewer's Comments		***Method acceptable, in future applicant needs to document full validation data***

Study Abstract Sheet: Study No. VR99.1203 (Supportive)

Name of Investigational Pr (Helioblock SX Cream)	**Name of Active Ingredient:** 3% Ecamsule + 10% Octocrylene + 2% Avobenzone + 5% Titanium Dioxide	**Indication:** Prevention of Polymorphous Light Eruption (PMLE)
Title of Study: Dermal absorption of [14C]-ecamsule (Meroxyl ® SX) and excretion of radioactivity in human volunteers		
Principal Investigators: Meuling, W.J.A., Vink, A.A., Klopping-Ketelaars W. A. A, Bie, A. Th. H. J		
Study Centers: TNO Nutrition and Food Research Institute, Department of Target Organ Toxicology, Netherlands		
Objectives: The purpose of this study was to determine the extent of absorption and excretion of radioactivity in humans after dermal application of a [14C]-Mexoryl SX ® containing cream.		
Design of Study: Phase I, open single-dose study		
Study Population Demographics: 5M, Age Range 19-29, All Caucasian, Wt = 62.2 – 74.3 kg, Height=175.1-187.3 cm		
Investigational Product: [14C]-Mexoryl SX ®[final concentration=2.02%, radioactivity per package = 18.5 MBq]. Formulation No. from L'Oreal, France.		
Dosing Regimen, Mode of Administration and Treatment Duration: An area of 100 cm^2 (5.95 x 16.90 cm) was delineated on one forearm for each volunteer, 200 mg of the test formulation was applied to this area with a disposable spatula and spread out using a finger cot. The treated area was covered with a dome made of perforated aluminium. Duration of the exposure was 4 hours, and subjects were confined during this period. The equivalent mcg [14C]-Mexoryl SX ®ranged from 37.62-38.83 mcg.		
Skin wash sample collection: At 4 hours after exposure, excess formulation is washed-off by wiping ten times with cotton wool rolls wetted with 5% sodiumlaurylethersulfate. The radioactivity in the wash off samples was then determined. **Urine sample collection:** Urine samples were collected at 0-4h, 4-12h and subsequently nine 12 h		

fractions up to 120 hours post dosing. **Blood sample collection:** 0, 1, 2, 3, 4, 6, 8, 10, 12, 14, 24, 34, 48, 72, 96 and 168 h after application. **Feces sample collection:** Complete stool was collected into plastic containers, after the start of the dermal application up to 120 h after start of application. **Skin stripping sample collection:** Samples of the stratum corneum and underlying epidermal cells were taken on study day 6 at about 120h after start of application. Approximately, 13-16 strips per subject were taken, and these comprised 31% of the total test area. **Analytical Methods**: Radioactivity was determined by liquid scintillation techniques. However, radioactivity of blood and feces samples was analyzed by combustion analysis and the CO_2 formed was then absorbed and mixed with scintillation liquid and the radioactivity determined. **Statistical Analysis:** Descriptive statistics
Summary Conclusions (see results in table below): The amount of radioactivity in the samples as a % of applied dose is as follows: **Skin wash**=91.52 ± 1.61, Blood and Feces = Nothing above background, Urine = 0.011 ± 0.003, Skin Strips = 0.008 ± 0.005, Dome = 0.073 ± 0.075, Gauze = 0.151 ± 0.135, Total = 91.91 ± 1.66. Highest levels were observed in urine fractions 4-12h and 12-24h after exposure. The mean % of ecamsule available for systemic absorption estimated from the % of applied dose of urine and feces excretion data and the skin stripping data was (0.011 % + 0 % + 0.008 % =0.019% i.e. ~ 0.02 % of the applied dose).
Safety: No drug related systemic or local effects due to [14C] Mexoryl® SX formulation was observed.

Study Abstract Sheet: Study No. V3156 (Supportive)

Name of Investigational Pr [redacted] (Helioblock SX Cream)	**Name of Active Ingredient:** 3% Ecamsule + 10% Octocrylene + 2% Avobenzone + 5% Titanium Dioxide	**Indication:** Prevention of Polymorphous Light Eruption (PMLE)
Title of Study: Urinary Excretion of Mexoryl® [SX] after repeated dermal applications of cream containing Mexoryl® [SX] in human volunteers		
Principal Investigators: Meuling, W.J.A., Roza L, Klopping-Ketelaars W.A.A, Viersen H.		
Study Centers: TNO Nutrition and Food Research Institute, Department of Target Organ Toxicology, Netherlands		
Objectives: To determine the systemically absorbed dose measured via the extent of urinary excretion of Mexoryl ® SX in man after repeated dermal application of a formulation containing Mexoryl ® SX.		
Design of Study: Open, multiple-dose study		
Study Schedule: June 25-30, 2001		
Study Population Demographics: 7M, Age Range 19-41, All Caucasian, Wt = 68.2 – 103.5 kg, Height=174.0-200 cm		
Investigational Product: ***W/O cream different from Helioblock SX Cream formulation, containing 4.95% of ecamsule-formulation*** [redacted] ***(inactive ingredients are similar to that included in the 2% [14 C] cream).****Reviewer's Comments: Ecamsule concentration is much higher than in Helioblock-SX cream. Data are purely supportive of minimal systemic exposure even at higher concentrations of ecamsule.*		
Dosing Regimen, Mode of Administration and Treatment Duration: Approximately 9.3-10.4 g was applied to the back and front (range 3321 – 4851 cm^2) once daily (dose rate = 0.002-0.003 g/cm^2 same as 2% cream) and spread out using a disposable glove. Before the next application on study days 2-5, the skin was washed with a moist cotton cloth dipped in a solution of 5% aqueous sodium lauryl ether sulfate. Then the subjects took a shower bath. After approximately 0.5 hour the subjects were asked to wear a cotton T-shirt for the next ~ 23 hours.		
Urine sample collection: before application, 0-4, 4-8, 8-12, 12-16, 16-24, 24-48, 48-72, 72-96, 96-100, 100-104, 104-108, 108-112, and 112-120 h **Skin wash and T-shirt sample collection:** Day 02, 03, 04, 05, and 06 at ~ 23h after topical application of the study substance. **Analytical Methods**: Mexoryl ® SX was determined in extracted samples of the T-shirts, skin and urine by HPLC-UV (343 nm) analysis. It was extracted from urine using [redacted]		

[redacted]. For the T-shirt and the skin wash the concentrations were calculated on the calibration line in mg/ l, corrected for the volume of extraction liquid that is used, and expressed in mg. LOQ was 4.9 ng/ml in urine, 0.61 mg/T-shirt and 0.07 mg/skin wash. Precision was 1.99-4.80 % for urine, 1.94 – 9.82 % for T-shirts, 0.55-2.89 % for skin wash.

Statistical Analysis: Descriptive statistics

Summary Conclusions: There was no quantifiable amount of ecamsule in any urine sample following repeated application of a 4.95% cream. Since the LOQ is relatively high, this data is limited in its interpretation. Cumulative mean (CV %) amount recovered from the T-shirts and skin wash were 61.2 (4) % and 13.5 (26) % of the applied dose respectively. Applicant states that amount not recovered was ~ 25.3% may be due to adherence to skin, retention in stratum corneum, loss by perspiration, skin turn-over, or contact with sheets during the night.

Safety: No drug related systemic or local effects due to ecamsule 4.95% topical application was reported.

Study Abstract Sheet: Study No. RDS.03.SRE.4689 In vitro (Supportive)

Name of Investigational Pr [redacted] (Helioblock SX Cream)	**Name of Active Ingredient:** 3% Ecamsule + 10% Octocrylene + 2% Avobenzone + 5% Titanium Dioxide	**Indication:** Prevention of Polymorphous Light Eruption (PMLE)

Title of Study: Comparison of the in vitro liberation-penetration of the UV filter ecamsule incorporated in four different formulations through human skin.

Study Centers: Galderma R & D Cedex, France

Objectives: The purpose of this study was to perform a pharmaceutical bioequivalence study by comparing the in vitro liberation-penetration of the UV filter ecamsule incorporated in four different formulations through human skin.

Design of Study: In vitro

Study Schedule: July 2000-October 2000

Investigational Products: (Octocrylene = O, Avobenzone = A, Ecamsule = E, Tita
Helioblock SX Cream : O:A:E:T; 10:2:3:5, [redacted]5: O:A:E:T; 10:2:2;2 [redacted]F [redacted]: O:A:E:T; 10:2:3;0, [redacted]5: O:A:E:T; 10:2:2;0
Reviewer's comments: [redacted]

Method: Six human mammary or abdominal skin samples from different donors were used to compare the four formulations. [redacted] At the end of the experiment the ecamsule concentrations were determined in the stratum corneum, epidermis, dermis and the receptor fluid using an HPLC/MS/MS. The product excess remaining on the skin was also quantified in order to evaluate mass balance. **Statistical Analysis:** An analysis of variance with effects for cell, experiment, and formulation on log transformed variables (i.e. quantities applied, excess, epidermis, skin [dermis+epidermis+stratum], skin thickness) and 90 % CI for the ratios between geometric means obtained. *[Reviewer's comment: What is the clinical relevance of the 16-hour application duration since product is to be applied prn in actual use? Maybe applicant could have applied two 8-hr applications instead]*

Results: Method validation was as follows: Precision (CV< 11%), Accuracy (% error < 19 %), Linearity 2-100 ng/mL (r > 0.9991) and 50 to 5000 ng/5 strips (r> 0.9985).

TABLE B: Ecamsule per cm² of skin: µg
(Arithmetic mean values ± SEM, N = 12)

	Formulation tested			
	A: Helioblock SX Cream [760.001]	B: [539.106]	C: [760.006]	D: [539.009]
ecamsule concentration (w/w)	3%	2%	3%	2%
Real applied dose	286.2 ± 11.0 µg	179.6 ± 3.4 µg	272.0 ± 6.2 µg	202.6 ± 5.1 µg
Surface excess	276.4 ± 16.4 µg	170.2 ± 8.8 µg	263.4 ± 12.4 µg	188.2 ± 6.9 µg
% of the applied dose	*97 %*	*95 %*	*97 %*	*93 %*
Stratum corneum: S	1.41 ± 0.44 µg	0.93 ± 0.12 µg	1.81 ± 0.31 µg	1.06 ± 0.31
% of the applied dose	*0.49 %*	*0.51 %*	*0.67 %*	*0.51 %*
Epidermis: E	1.01 ± 0.40 µg	0.74 ± 0.26 µg	0.64 ± 0.15 µg	0.34 ± 0.06 µg
% of the applied dose	*0.33 %*	*0.40 %*	*0.24 %*	*0.17 %*
Dermis: D	0.02 ± 0.01 µg	0.07 ± 0.06 µg ③	0.02 ± 0.01 µg	0.01 ± 0.01 µg ④
% of the applied dose	*0.01 %*	*0.04 %*	*0.01 %*	*0.01 %*
(1)Total skin: S+E+D	2.44 ± 0.58 µg	1.74 ± 0.30 µg	2.46 ± 0.40µg	1.41 ± 0.32 µg
% of the applied dose	*0.83 %*	*0.96 %*	*0.92 %*	*0.69 %*
(2) Collected fraction	0.003 ± 0.002② µg	0.27 ± 0.27③ µg	0.002 ± 0.001① µg	0.001± 0.001① µg
% of the applied dose	*0.001 %*	*0.16 %*	*0.001 %*	*0.0003 %*
(1+2) Total penetrated	2.45 ± 0.58 µg	2.01 ± 0.42 µg	2.46 ± 0.40 µg	1.41 ± 0.32 µg
% of the applied dose	*0.83 %*	*1.1 %*	*0.92 %*	*0.69 %*
Mass balance	278.8 ± 16.4 µg	172.2 ± 8.8 µg	265.9 ± 12.2 µg	189.6 ± 6.9 µg
% of the applied dose	*97 ± 4 %*	*96 ± 5 %*	*98 ± 5 %*	*94 ± 3 %*

① *11 values out of 12 are BLQ*
② *10 values out of 12 are BLQ*
③ *9 values out of 12 are BLQ*
④ *8 values out of 12 are BLQ*
BLQ: below the limit of quantification (< 2 ng.mL⁻¹)

Statistical data for quantities that penetrated through the skin (dermis, epidermis and stratum corneum)

Formulation Comparisons*	Ratio	90% CI	p-value
A vs. B	1.23	0.72, 2.11	0.513
A vs. C	0.85	0.49, 1.46	0.608
A vs. D	1.58	0.92, 2.71	0.158

*A=Helioblock SX cream, B= , C , D =

Summary Conclusions:
Ecamsule was distributed mainly in the stratum corneum with the cream (without titanium dioxide) having the highest values. The ecamsule levels recovered in the dermis were low (≤ 0.04% of the applied dose). The total amounts of ecamsule that penetrated the skin (stratum corneum, epidermis, dermis, receptor fluid) were < 1% of the applied dose. The statistical analysis showed that there were no significant differences between the four formulations (p > 0.05) with regards to the penetration of ecamsule. However, the variability was very high as shown by the large 90% CI. Also there was high

experimental variability for the epidermis (97 % coefficient of variation), 79 % for the stratum and 77 % for skin (See tables below for details. Note that skin =dermis +epidermis + stratum corneum)).

TABLE S2 - Geometric mean for each formulation and ratio estimates with their 90% confidence interval

Form1	Form2	VARIABLE	LSMEAN Form1	LSMEAN Form2	p-value	Form1/Form2 Ratio	Lower limit	Upper limit
A	B	THICKNESS	1.122	1.076	0.016	1.04	1.01	1.07
		EPIDERMIS	0.546	0.327	0.213	1.67	0.84	3.29
		EXCESS	270.318	171.055	0.000	1.58	1.44	1.73
		% RECOVERY (1)	96.222	95.716	0.918	1.01	0.92	1.10
		QUANTITY APPLIED	283.522	180.474	0.000	1.57	1.48	1.66
		SKIN	1.719	1.393	0.513	1.23	0.72	2.11
		STRATUM	0.846	0.788	0.829	1.07	0.62	1.87

TABLE S2 - Geometric mean for each formulation and ratio estimates with their 90% confidence interval

Form1	Form2	VARIABLE	LSMEAN Form1	LSMEAN Form2	p-value	Form1/Form2 Ratio	Lower limit	Upper limit
A	C	THICKNESS	1.122	1.062	0.002	1.06	1.03	1.09
		EPIDERMIS	0.546	0.471	0.720	1.16	0.58	2.31
		EXCESS	270.318	261.522	0.556	1.03	0.94	1.14
		% RECOVERY (1)	96.222	97.220	0.842	0.99	0.91	1.08
		QUANTITY APPLIED	283.522	271.683	0.226	1.04	0.98	1.11
		SKIN	1.719	2.031	0.608	0.85	0.49	1.46
		STRATUM	0.846	1.416	0.129	0.60	0.34	1.05

TABLE S2 - Geometric mean for each formulation and ratio estimates with their 90% confidence interval

Form1	Form2	VARIABLE	LSMEAN Form1	LSMEAN Form2	p-value	Form1/Form2 Ratio	Lower limit	Upper limit
A	D	THICKNESS	1.122	1.087	0.059	1.03	1.00	1.06
		EPIDERMIS	0.546	0.280	0.107	1.95	0.99	3.85
		EXCESS	270.318	183.212	[illegible]	1.47	1.34	1.62
		% RECOVERY (1)	96.222	92.178	0.[illegible]	1.04	0.96	1.14
		QUANTITY APPLIED	283.522	200.451	0.000	1.41	1.34	1.50
		SKIN	1.719	1.086	0.158	1.58	0.92	2.71
		STRATUM	0.846	0.635	0.384	1.33	0.77	2.32

TABLE S1 - Residual standard deviation (error within cell, experiment and form) and significance of formulation, experiment and cell effects

VARIABLE	Residual SD	p-value Formulation	p-value Experiment	p-value Cell
THICKNESS	0.039	0.015	0.000	0.000
EPIDERMIS	0.971	0.319	0.008	0.820
EXCESS	0.132	0.000	0.005	0.064
% RECOVERY (1)	0.122	0.738	0.003	0.516
QUANTITY APPLIED	0.082	0.000	0.023	0.286
SKIN	0.767	0.239	0.305	0.285
STRATUM	0.787	0.109	0.026	0.055

Study Abstract Sheet: Study No. 16039/G2347 In vitro (Supportive)

Name of Investigational Pr [redacted] (Helioblock SX Cream)	**Name of Active Ingredient:** 3% Ecamsule + 10% Octocrylene + 2% Avobenzone + 5% Titanium Dioxide	**Indication:** Prevention of Polymorphous Light Eruption (PMLE)

Title of Study: In vitro percutaneous absorption of [14C]-G2347 formulated in a W/O Sunscreen Emulsion

Study Centers: L'Oreal, France

Objectives: The purpose of this study was to describe the in vitro percutaneous absorption and distribution of Mexoryl SX (G2347) on human skin. Its ultimate purpose is to compare the absorption results with in vivo data obtained in humans following the topical application of the same formulation for 4 hours under similar experimental conditions (i.e. Study V99.1203).

Design of Study: In vitro

Investigational Products: Formulation No [redacted] containing 2% of [14-C]-Mexoryl SX. Concentration of radiolabeled and unlabelled = 1.946 (0.008) %.

Method: Sample of human skin (obtained from the abdominal skin flaps of female subjects aged 47-62 years old) were dermatomed and mounted in static mode diffusion cells (N=16). Amount applied per cm^2 ranged from 1.995 – 3.905 mg. After 4 hours application the surface of the skin was washed using 600 mcl of 5% sodium lauryl sulfate followed by 600 mcl of distilled water (twice). Twenty-four hours after application, the cells were dismounted and the samples were analyzed). The quantities of ecamsule in the following compartments were then analyzed: Surface excess washings at t=4 hours, stratum corneum (strippings of stratum corneum at t = 24 hours), Malpighian (epidermis) layer +partial dermis at t = 4 and 24 hours, Receptor liquid (volume of the lower compartment of the diffusion cell at t =4 and 24 hours). The quantity absorbed is defined as the total quantity in the epidermis+partial dermis+receptor liquid. Assay Method and Validation: Reversed Phase HPLC with UV detection @342 nm.

Results:

Table IV : Cutaneous distribution of [^{14}C]-G2347 and/or [^{14}C] derivatives formulated in a W/O sunscreen emulsion, means ± SD in % of applied dose and in $\mu g_{eq}/cm^2$

Skin compartments (mean ± SD)	W/O emulsion applied for 4 hours N°291 857	
	4 hours' desorption (n=8)	24 hours' desorption (n=8)
Surface excess µg$_{eq}$/cm² % of applied dose	52.28 ± 11.92 95.15 ± 4.07	54.52 ± 12.52 101.10 ± 4.14
Stratum corneum µg$_{eq}$/cm² % of applied dose	0.08 ± 0.08 0.14 ± 0.11	0.10 ± 0.10 0.19 ± 0.15
Malpighian layer µg$_{eq}$/cm² % of applied dose	0.05 ± 0.03 0.08 ± 0.05	0.14 ± 0.10 0.25 ± 0.18
Malpighian layer + SC µg$_{eq}$/cm² % of applied dose	0.13 ± 0.11 0.22 ± 0.14	0.23 ± 0.19 0.41 ± 0.30
Partial dermis µg$_{eq}$/cm² % of applied dose	0.03 ± 0.04 0.06 ± 0.06	0.05 ± 0.07 0.09 ± 0.10
Receptor liquid µg$_{eq}$/cm² % of applied dose	0.06 ± 0.07 0.10 ± 0.11	0.04 ± 0.03 0.07 ± 0.07
% total	95.51 ± 4.02	101.66 ± 4.13
Quantity = total skin + + RL* µg$_{eq}$/cm² % of applied dose	0.21 ± 0.15 0.38 ± 0.20	0.32 ± 0.25 0.56 ± 0.35
Quantity absorbed** µg$_{eq}$/cm² % of applied dose	0.13 ± 0.10 0.22 ± 0.15	0.21 ± 0.17 0.37 ± 0.23

SC : stratum corneum ; M layer : Malpighian layer ; D : Partial dermis ; RL : Receptor liquid
* Quantity = total skin = + RL : sum of the quantities = SC + M layer + D = + RL
** Quantity = absorbed = : sum of the quantities = M layer + D = RL =

Summary Conclusions: The % of applied dose that penetrated was 0.36 (0.20) % and 0.56 (0.35) % after 4 hours application and, 24 hours of exposure, respectively. This value is much higher than that obtained in vivo (~0.02%, see table 5 and summary conclusions of study No. VR99.1203 that used the same formulation as the one used in this study), suggesting that the in vitro data does not really correlate with in vivo conditions. There was a high variability associated with the in vitro data inherent in the differences in skin thickness (ranging from 286 to 497 micrometers) for different donors. The applicant stated that the quantities absorbed were similar for the 4 hr and 24 hr periods because the time of application of the formulation was the same for both experimental series. The difference in the skin distribution (higher In epidermis after 24 hours compared to 4 hours) of ecamsule between the two application periods corresponds to a passive diffusion gradient through the skin.

Study Abstract Sheet: Study No. 16096 In vitro (Supportive)

Name of Investigational Pr [redacted] (Helioblock SX Cream)	**Name of Active Ingredient:**\3% Ecamsule + 10% Octocrylene + 2% Avobenzone + 5% Titanium Dioxide	**Indication:** Prevention of Polymorphous Light Eruption (PMLE)

Title of Study: Effects of Pigments on the Cutaneous Absorption In Vitro of Parsol 1789 and mexoryl SX
Study Centers: L'Oreal Advanced Research Laboratories, Department of Life Sciences, Cedex, France
Objectives: To evaluate the effect of Titanium dioxide (TiO^2) pigments on the transcutaneous absorption of avobenzone and Mexoryl SX introduced into an O/W emulsion containing other filters, in vitro.
Design of Study: In vitro (Study finalized on October 31, 2002)
Investigational Products: An Arlacel 165 O/W emulsion containing a combination of filters with (formulation No. [redacted]) and, without (formulation No. [redacted]) pigments. The formula was as follows: Avobenzone (3.5%), Mexoryl SX (3 %), Octocrylene (10 %), Mexoryl XL (3.5%) and titanium dioxide (5% for pigmented formulation only).

Table IV. Continuous distribution of avobenzone and Mexoryl SX formulated in an O/W emulsion with and without pigments, means and standard deviations, in % of the dose applied and in µg/cm2

	Avobenzone		Mexoryl SX	
Cutaneous compartment (mean ± S.D.	No. 292869 (n = 8)	No. 43577691 TiO_2 (n = 8)	No. 292869 (n = 6)	No. 43577691 TiO_2 (n = 8)
Surface area excess				
µg/cm²	174.57 ± 28.10	172.42 ± 26.93	159.63 ± 23.09	150.05 ± 24.10
% of applied dose	93.84 ± 2.92	93.05 ± 4.18	93.43 ± 4.41	93.01 ± 4.54
Stratum corneum	3.14 ± 2.45	1.93 ± 1.42	0.09 ± 0.05	0.22 ± 0.23
µg/cm²	1.64 ±1.14	1.00 ± 0.61	0.05 ± 0.03	0.13 ± 0.13
% of applied dose				
M. ep. + dermis				
µg/cm²	1.80 ± 0.75	1.82 ± 0.91	0.02 ± 0.02	0.03 ± 0.03
% of applied dose	1.01 ± 0.51	0.98 ± 0.48	0.01 ± 0.01	0.02 ± 0.02
Total skin**				
$\mu g_{equ}/cm^2$	4.94 ± 2.87	3.76 ± 2.06	0.11 ± 0.07	0.25 ± 0.26
% of applied dose	2.65 ± 1.40	1.98 ± 0.90	0.06 ± 0.04	0.15 ± 0.15
$\mu g_{equ}/cm^2$	0.02 ± 0.02	0.01 ± 0.02	0.00 ± 0.00	0.00 ± 0.00
% of applied dose	0.01 ± 0.01	0.00 ± 0.01	0.0 ± 0.00	0.0 ± 0.00
Balance, %	96.49 ± 2.86	95.04 ± 4.03	93.49 ± 4.41	93.16 ± 4.57
Quantity absorbed*				
$\mu g_{equ}/cm^2$	1.82 ± 0.76	1.83 ± 0.91	0.02 ± 0.02	0.03 ± 0.03
% of applied dose	1.02 ± 0.52	0.98 ± 0.48	0.01 ± 0.01	0.02 ± 0.02
Total skin quantity** + RL				
$\mu g_{equ}/cm^2$	4.95 ± 2.87	3.77 ± 2.07	0.11 ± 0.07	0.25 ± 0.26
% of applied dose	2.66 ± 1.41	1.98 ± 0.90	0.06 ± 0.04	0.15 ± 0.15

SC: stratum corneum. M. Ep.: malpighian epidermis. RL: receptor liquid. *Quantity absorbed: M. Ep. combined with full-thickness dermis + RL. **Total skin quantity: SC + malpighian epidermis + full-thickness dermis; S.D.: standard deviation.

Method: The experiments were conducted on human skin samples isolated in a static diffusion cell. The formulations were applied at a rate of ~5 mg/cm^2. Only the absorption and penetration of avobenzone and Mexoryl SX (ecamsule) were determined after 16 hours of application. The variables analyzed were [A] the quantities of the two filters present 1) as surface excess 2) stratum corneum 3) malpighian layer of the epidermis + full-thickness dermis and 4) receptor fluid, [B] quantity absorbed = malpighian layer +dermis +receptor liquid, [C] Total Skin quantity = stratum corneum +malpighian layer+dermis+receptor liquid. Assay was by [redacted] HPLC method with UV detection @ 357 nm for avobenzone and 343 nm for ecamsule. LOQ = 0.010 mcg/mL for avobenzone and 0.05 mcg /mL for ecamsule.

Results: (see table below)

Avobenzone: The quantity absorbed (% of applied dose) were 1.02 (0.52) without pigment and 0.98 (0.48) with pigment. The quantity that penetrated (% of applied dose) was 2.66 (1.41) without pigment and 1.98 (0.90) with pigment.

Mexoryl SX: The quantity absorbed (% of applied dose) were 0.01 (0.01) without pigment and 0.02 (0.02) with pigment. The quantity that penetrated (% of applied dose) was 0.06 (0.04) without pigment and 0.15 (0.15) with pigment**.** The applicant stated that the difference between quantities that penetrated were not statistically significant ($p > 0.05$).

For both compounds the quantities analyzed in all the compartments (except the stratum corneum) were somewhat similar with or without the pigment. In the stratum corneum, it appears that the % applied of avobenzone decreased [1.64 (1.14) vs. 1.00 (0.61)] in the presence of the pigment and that of ecamsule increased [0.05 (0.03) vs. 0.13 (0.13)]. However, when one takes the variability into account the values are comparable as reflected in the lack of statistical significance in the difference observed for the total amount that penetrated.

Summary Conclusions:

Under the experimental conditions, the titanium dioxide pigment did not affect the percutaneous absorption of avobenzone or ecamsule incorporated into an O/W emulsion and co-formulated with other filters

Reviewer's Comments: Applicant inadvertently left out the Receptor Liquid title after total skin in the above table.

Study Abstract Sheet: Study No. 16059 In vitro (Supportive)

Name of Investigational Product:	**Name of Active Ingredient:**	**Indication:**
[redacted] (Helioblock SX Cream)	3% Ecamsule + 10% Octocrylene + 2% Avobenzone + 5% Titanium Dioxide	Prevention of Polymorphous Light Eruption (PMLE)

Title of Study: In vitro Transcutaneous Absorption of Parsol 1789 Formulated in Solar Development Vehicles

Study Centers: L'Oreal Advanced Research Laboratories, Department of Life Sciences, Cedex, France
Objectives: To compare the cutaneous penetration and distribution of Parsol 1789 formulated at 3.72 % in three solar development vehicles and a reference formulation
Design of Study: In vitro
Investigational Products: No 292266 (the oil/water emulsion) No. 292263 (water/oil milk), No. 292.264 (the cream gel), and No. 292 265 (the 700AO base) with 3.72 % Parsol 1789 were prepared in the Solar Department Laboratory. The actual concentrations of Parsol 1789 ranged from 3.77 (0.5) to 3.95 (0.05).
Method: The experiments were conducted on human skin samples isolated in a static diffusion cell. The formulations were applied at a rate of ~5 mg/cm^2. The absorption and penetration of avobenzone was determined after 16 hours of application. The variables analyzed were [A] the quantities of the two filters present 1) as surface excess 2) stratum corneum 3) malpighian layer of the epidermis + full-thickness dermis and 4) receptor fluid, [B] quantity absorbed = malpighian layer +dermis +receptor liquid, [C] Total Skin quantity = stratum corneum +malpighian layer+dermis+receptor liquid. Assay was by reversed phase HPLC method with UV detection @ 357 nm for avobenzone. LOQ = 0.010 mcg/mL for avobenzone.
Results: (see table below) The quantities absorbed were different for the different vehicles with the 700AO base having the lowest (least lipophilic) and the cream gel having the highest (most lipophilic). The total quantities that penetrate also follow the same pattern. However the quantities recovered (range of % of the applied dose = 0.01-0.04) in the receptor liquid were somewhat comparable for all four vehicles when one takes the variability into account.
Summary Conclusions: The percentage of the applied dose of avobenzone that penetrated into the receptor liquid was minimal (<0.04%). Also the amount that was absorbed, though different for the different vehicles was minimal (< 3%). The quantity absorbed for these formulations (especially the O/W emulsion using Aracel 165) is higher than what was obtained with the combination product of avobenzone with other filters using the same methodology in Study 16096. This may be due to the differences in the formulations with regards to the concentration of avobenzone and the excipients as well as the variability due to the differences in skin from different donors. This implies that caution should be exercised in making any inferences that address both sets of data together.

Table IV. — Cutaneous distribution of Parsol 1789 formulated in four solar formulation vehicles, with means and standard deviations expressed as a percentage of the applied dose and in µg/cm².

Skin compartments Mean ± standard deviation	W/O No. 292 263 (n = 8)	Cream gel No. 292 264 (n = 8)	700-AO base No. 292 265 (n = 6)	O/W No. 292 266 (n = 8)
Surface excess µg/cm²	174.00 ± 34.93	158.44 ± 15.18	169.76 ± 17.56	162.21 ± 23.82
% of the applied dose	93.89 ± 3.51	85.69 ± 5.66	96.38 ± 1.73	93.32 ± 6.76
The *stratum corneum* µg/cm²	6.51 ± 3.72	12.39 ± 5.14	1.60 ± 1.24	6.49 ± 4.59
% of the applied dose	3.48 ± 1.61	6.49 ± 2.19	0.92 ± 0.73	3.87 ± 2.61
Mal. ep. + dermis µg/cm²	2.99 ± 1.73	4.26 ± 1.60	0.73 ± 0.36	2.34 ± 1.07
% of the applied dose	1.75 ± 1.40	2.26 ± 0.78	0.41 ± 0.20	1.39 ± 0.73
Stratum corneum + Mal. ep. + dermis $\mu g_{eq}/cm^2$	9.50 ± .97	16.65 ± 6.39	2.34 ± 1.55	8.83 ± 5.39
% of the applied dose	5.23 ± 2.69	8.75 ± 2.75	1.34 ± 0.91	5.26 ± 3.16
Receptor liquid $\mu g_{eq}/cm^2$	0.02 ± 0.02	0.05 ± 0.07	0.02 ± 0.02	0.07 ± 0.06
% of the applied dose	0.01 ± 0.01	0.02 ± 0.03	0.01 ± 0.01	0.04 ± 0.04
Overall total, in %	99.14 ± 1.49	94.46 ± 3.93	97.73 ± 1.84	98.63 ± 6.40
Quantity absorbed* $\mu g_{eq}/cm^2$	3.01 ± 1.72	4.30 ± 1.60	0.76 ± 0.37	2.42 ± 1.08
% of the applied dose	1.77 ± 1.40	2.28 ± 0.78	0.43 ± 0.21	1.43 ± 0.73
Quantity: Total skin + the receptor liquid $\mu g_{eq}/cm^2$	9.52 ± 4.96	16.70 ± 6.42	2.36 ± 1.57	8.91 ± 5.41
% of the applied dose	5.24 ± 2.69	8.77 ± 2.76	1.35 ± 0.92	5.31 ± 3.17

Mal. ep.: malpighian epidermis.
*Quantity absorbed: The malpighian epidermis in association with the full-thickness dermis and the receptor liquid
**Total skin quantity: *Stratum corneum* + malpighian epidermis + full-thickness dermis

Reviewer's comments on other additional studies:

The applicant also conducted two non-GLP in vitro studies to measure the penetration of ecamsule 5% (rats and humans) or 10% (humans only) through the hairless rat and human dermatomized skin samples, mounted in modified static Franz cells. The data for these studies were not reviewed because they did not provide any additional data that had not already been provided by the in vivo studies also the concentrations of ecamsule and formulation used were outside the range proposed for marketing.

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	22-009	**Brand Name**	Helioblock® SX Sunscreen Cream (SPF 40)
OCPB Division (I, II, III)	DCP 3	**Generic Name**	Ecamsule [Mexoryl® SX] 3%, Avobenzone 2%, Octocrylene 10%, and Titanium dioxide, 5%
Medical Division	ONP	**Drug Class**	Sun Screen
OCPB Reviewer	Abi Adebowale	**Indication(s)**	To prevent sunburn [redacted] following [redacted] exposure to ultraviolet radiation (UVR)
OCPB Team Leader	Lydia Velazquez	**Dosage Form**	Cream

		Dosing Regimen	Apply evenly 15 minutes before sun exposure. Re-apply as needed or after towel drying, swimming or perspiring. Children under 6 months of age: ask a doctor
Date of Submission **Filing Date**	31st , May, 2007 30th, , July, 2007	**Route of Administration**	Topical
Estimated Due Date of OCPB Review	15th, February, 2008	**Sponsor**	L'OREAL USA Products, Inc. NJ
PDUFA Due Date	31st, March 2008	**Priority Classification**	Standard
		IND Number	59, 126 and 57,850

Clin. Pharm. and Biopharm. Information

	"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			Incorporated in the study reports
I. Clinical Pharmacology				
Mass balance:	X	1		V99.1203 (cream containing 2% of [^{14}C]-ecamsule.
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1A		1.CG.03.SRE.2607 (used Helioblock SX cream consisting of Ecamsule [Mexoryl® SX] 3%, Avobenzone 2%, and Octocrylene 10%) and Titanium dioxide 5 %
multiple dose:	X	1A and 1		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	4		RDS.03.SRE.4689 (evaluated three [redacted] OTC products including [redacted] SPF 15 Lotion and also Helioblock ® SX Cream) and 16039/G2347 (cream containing 2% of [^{14}C]-ecamsule). Study No. 16059 and 16096
Chronopharmacokinetics				
Pediatric development plan	**X**			Partial waiver request for pediatric studies in children less than 6 months of age for the prevention of sunburn. Clinical safety data in children aged 6 months to < 18 years old.
Literature References		**3**		
Total Number of Studies		**7**	**7**	

Filability and QBR comments		
	"X" if yes **X**	**Comments** All the Systemic Exposure data included in this submission are the same as that already reviewed in approvable NDA # [redacted] approved NDA #'s 21-501, 21-502 and 21-471. Note that a PREA Partial Waiver was granted for NDA #'s 21-501, 21-502 and 21-471 for pediatric studies in children less than 6 months of age for the prevention of sunburn. No new Clinical Pharmacology or Biopharmaceutics information was included in this submission compared with the previously approved NDAs.
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 in vivo bioavailability of Helioblock SX Sunscreen cream (SPF 40) under maximal use conditions?	
Other comments or information not included above		
Primary reviewer Signature and Date	**Abi Adebowale**	
Secondary reviewer Signature and Date		

CC: NDA 22-009, HFD-850 (P.Lee), ONP (E.Abraham), DCP 3 (L.Velazquez, H. Ahn)

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

/s/

Abi Adebowale
2/15/2008 04:46:23 PM
BIOPHARMACEUTICS

Lydia Velazquez
2/19/2008 01:05:58 PM
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